BENZOTRIAZOLE-MEDIATED SYNTHESIS OF HETEROCYCLES

By

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To my parents and my wife, Jingting, with love

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A variety of heterocycles have been synthesized using benzotriazole as an organic auxiliary: a good leaving group, an activating group to proton loss and a good radical precursor.

N,N-Bis[(benzotriazol-1-yl)methyl]benzylamines functioned as novel 1,3-dication equivalents in reactions with allyltrimethylsilane or substituted allyltrimethylsilanes (which are 1,3-dianion equivalents) affording substituted piperidines in good yields. On the other hand, *N,N*-bis[(benzotriazol-1-yl)methyl]anilines (unsubstituted and *p*-CH_3, OCH_3, Cl) gave julolidine analogues.

Polysubstituted piperidines were prepared *via* intramolecular radical cyclization of α-aminoalkyl radicals onto unactivated double bonds. Major products were assigned as having *cis* geometry based on NMR. Major conformation of *cis* products were determined by NMR. The [1,2]-aza-Wittig rearrangements were observed. Further studies involved compounds with an aryl group attached to the α-aminoalkyl radical center.

Lithiation of *N*-Boc-*N*-(benzotriazol-1-ylmethyl)benzylamine gave a dipole-stabilized carbanion with two *N*-linked substituents, which reacted with imines to afford *trans*-4,5-disubstituted imidazolidin-2-one benzotriazole derivatives in good yields and with excellent *trans*-stereoselectivity. Subsequent substitution of the benzotriazole moiety in these 4,5-disubstituted imidazolidin-2-ones by various nucleophiles (zinc reagents, allyltrimethylsilane and vinyloxysilanes) in the presence of a Lewis acid gave exclusively *trans*-4,5-disubstituted imidazolidin-2-ones in good yields. Thus, *N*-Boc-*N*-(benzotriazol-1-ylmethyl)benzylamine as a 1,1-dipole equivalent enabled the preparation of various *trans*-4,5-disubstituted imidazolidin-2-ones.

The dipole-stabilized carbanion generated from *N*-Boc-*N*-(3-halopropyl) (benzotriazol-1-ylmethyl)amine cyclized to afford the key intermediate 2-benzotriazolyl-*N*-Boc-pyrrolidine, which underwent nucleophilic displacement of the benzotriazolyl group to afford various 2-substituted-*N*-Boc-pyrrolidines in good yields.

Alkylzinc reagents, in contrast to arylzinc reagents, reacted with two series of α-benzotriazolylalkylamines to give oxidized products formed by the incorporation of an atom of oxygen into the carbon-zinc bond even when the reactions were carried out under argon. Thus, benzotriazole derivatives of 4,5-disubstituted imidazolidin-2-one and *N*-Boc-2-benzotriazolyl pyrrolidine gave oxidized products, respectively. The abnormal reaction course was traced to molecular oxygen dissolved in the THF. The expected, unoxidized heterocyclic products were obtained under rigorous argon purge of the THF solvents and solutions.

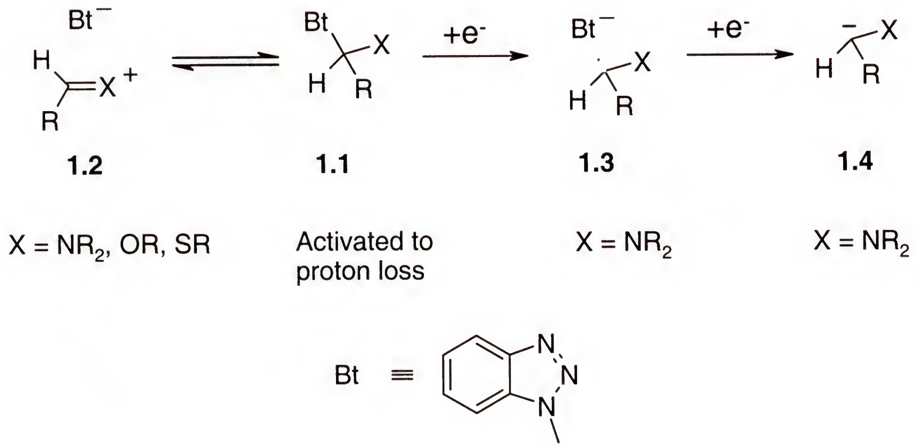
CHAPTER 1
GENERAL INTRODUCTION

Heterocycles play an important role in organic and pharmaceutical chemistry. Benzotriazole is a good organic auxiliary and offers many advantages in the synthesis of these heterocycles [98CR409]. Benzotriazole is an inexpensive and stable compound which can be easily recycled. It is very stable under various synthetic operations and can exert an activating influence on other parts of the molecule.

Many of *N*-substituted benzotriazole derivatives **1.1** are easily prepared and possess the typical properties as shown in Scheme 1.1. Benzotriazole has both electron-donating and electron-accepting properties, so compounds with a hetero-atom (most commonly N, O, S) at the α-position to the benzotriazole can ionize forming the benzotriazole anion and iminium, oxonium, or thionium cations **1.2**. Benzotriazole can activate the α-CH group in **1.1** toward proton loss**.** Single-electron reducing agents (such as SmI_2) can remove benzotriazole to form an α-amino radical **1.3**, which can be further reduced to the carbanion **1.4** using one more equivalent of the reducing reagents. Herein, we report the synthesis of several types of heterocyclic compounds using the benzotriazole properties listed above.

Using the property of a benzotriazole derivative to ionize to intermediate **1.2**, we demonstrate the usefulness of *N*,*N*-bis[(benzotriazol-1-yl)methyl]amines as novel 1,3-

dication synthons for the synthesis of substituted piperidines and julolidine analogues (Chapter 2).



Scheme 1.1

The ability of such benzotriazole derivatives to form intermediates **1.3** and **1.4** is applied in one-pot preparations of polysubstituted piperidines using 6-exo-α-aminoalkyl radical cycloadditions (Chapter 3), and also in the investigation of the sparsely studied [1,2]-aza-Wittig rearrangements (Chapter 3).

It is known that the presence of an α-activating group (X = OR, SR or Ar) makes benzotriazole derivatives **1.1** easy to lithiate at the α position to X, but the abstraction of the proton α to the nitrogen atom ($X = NR_2$, R = alkyl) in **1.1** has not yet successfully been realized. Benzotriazole-assisted formation of dipole-stabilized carbanions α to the nitrogen atom in **1.1** (X = N(Boc)R, R = alkyl) is now explored for the first time in both intermolecular (Chapter 4) and intramolecular reactions (Chapter 5). Thus, stereoselective synthesis of 4,5-disubstituted imidazolidin-2-ones (Chapter 4) and facile synthesis of 2-substituted *N*-Boc-pyrrolidines (Chapter 5) are reported both using dipole-stabilized carbanion intermediates.

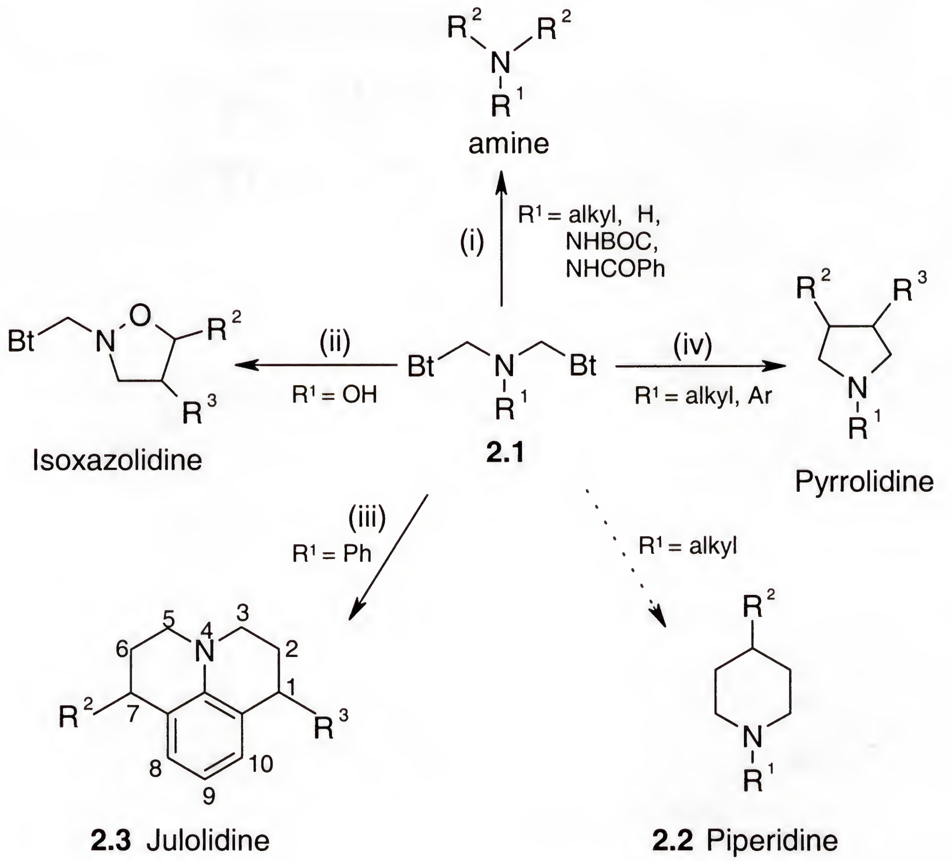
Due to the easy formation of intermediates **1.2**, nucleophiles can easily replace the benzotriazole moiety in **1.1** (Chapters 1, 4, 5 and 6). Organozinc reagents are the most widely used in such substitution reactions (Chapters 4 and 5). However, we found that alkylzinc reagents are remarkably easily oxidized during the preparation of substituted heterocycles (Chapter 6).

In summary, in this study we synthesized several classes of heterocycles using benzotriazole as a good organic auxiliary. This study includes the synthesis of substituted piperidines using both carbocation and radical chemistry, stereoselective construction of 4,5-disubstituted imidazolidin-2-ones and facile routes to 2-substituted *N*-Boc-pyrrolidines.

CHAPTER 2
SYNTHESIS OF SUBSTITUTED PIPERIDINES FROM *N,N*-BIS[(BENZOTRIAZOL-1-YL)METHYL]AMINES

2.1 Introduction

Syntheses of piperidines are well documented [88JOC5491, 98JOC566, 98JOC2711, 97T8447] due to their physical and biological properties and their presence in numerous natural products [85JMC1925, 85JMC1934, 85JMC1943, 84JMC1570, 83JMC1747, 85JMC699]. *N,N*-Bis[(benzotriazol-1-yl)methyl]amines **2.1**, readily prepared from 1-(hydroxymethyl) benzotriazole and amines or from benzotriazole, aqueous formaldehyde, and amines [87JCS(P1)799, 90CJC446], are useful (Scheme 2.1) in the preparation of: (i) Secondary and tertiary amines (R^1 = alkyl, H) [91S703, 94JOC5206], *N,N*-disubstituted hydroxylamines (R^1 = OH) [89JCS(1)225], 1,1-disubstituted hydrazines and their 2-acyl derivatives (R^1 = NHCOR) [89JCS(P1)2297], *via* displacement by Grignard reagents or $NaBH_4$ reduction of benzotriazole; (ii) Isoxazolidines (R^1 = OH) [90JCS(P1)2371] by conversion of bis[(benzotriazol-1-yl) methyl] hydroxylamine to the nitrone and 1,3-dipolar additions; (iii) Julolidines (R^1 = Ph) [96JOC3117], through elimination of benzotriazole, formation of methylene immonium cation, and subsequent reaction with two molecules of vinyl ether or vinyl amide; (iv) Pyrrolidines (R^1 = Ar, alkyl) [98H2535] by reductive cleavage of Bt-C bond by SmI_2 to generate dianion and reaction with alkenes. We now report the application of **2.1** for the synthesis of piperidines.



Scheme 2.1

The [3+3] cycloaddition reactions are important and useful in the syntheses of six-membered heterocyclic systems [84CHC(2)63, 79COC(2)3, 96JA4200, 94TL6461]. Most such reactions involve the condensation of a 1,3-dinucleophile (*e.g.* amidine, guanidine, urea, thiourea or sulfamide) with a 1,3-dielectrophile (*e.g.* 1,3-dicarbonyl compound, related species such as cyanoacetic esters and malononitriles, or α,β-unsaturated aldehydes, ketones, esters and nitriles). These [3+3] cycloaddition reactions are mainly used to synthesize aromatic heterocycles. However, Grieco *et al.* [86JA3512, 86TL5067, 87JCS(CC)185] elegantly prepared 4-hydroxypiperidines by a related

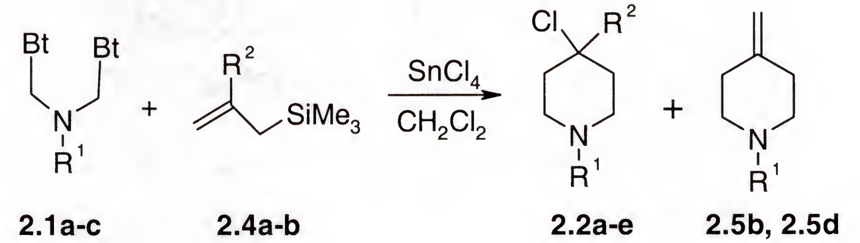
[3+1+1+1] reaction of allyltrimethylsilanes with *N*-benzylammonium trifluoro-acetate and aqueous formaldehyde in water.

In an extension of Grieco's work, we now show that 4-functionalized piperidines can be prepared by the reaction of **2.1** with allyltrimethylsilane: allyltrimethylsilane serves as a three-carbon dipole equivalent [88ACR200], and **2.1** as a nitrogen atom centered 1,3-dication synthon. Depending on the substitution pattern of **2.1**, allyltrimethylsilane can serve alternatively as an alkene to give julolidines by intramolecular electrophilic cyclization (Scheme 2.1).

2.2 Results and Discussion

Reaction of *N,N*-Bis[(benzotriazol-1-yl)methyl]alkylamines **2.1** with Allyltrimethylsilanes to Prepare Substituted Piperidines **2.2.** Compounds **2.1a-c** reacted with allyltrimethylsilanes **2.4a-b** in the presence of $SnCl_4$ to give 1,4-, and 1,4,4-substituted piperidines **2.2a-e** in 58-68% yields (Scheme 2.2). Compound **2.2a** was previously prepared by Grieco [86JA3512] in 48% yield by reacting benzylamine hydrochloride with aqueous formaldehyde and allyltrimethylsilane in the presence of lithium chloride.

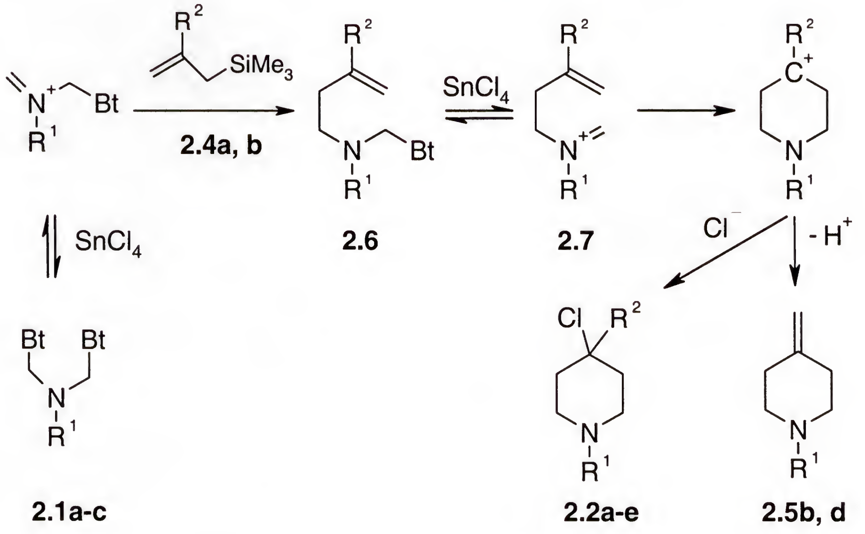
Reactions of **2.1a-b** with 2-methylallyltrimethylsilane **2.4b** gave both the products **2.2b,d** of chloride ion trapping and the elimination products **2.5b,d**. Compounds **2.2b,d** can be converted into compounds **2.5b,d** with either base or acid catalysts. Quenching the reaction with dry methanol instead of water reduced the percentage of product **2.5b** from 16% to 5% [84S960]. The mechanism of this reaction could be as shown in Scheme 2.2. Since only traces of the by-product homoallylamine **2.6** were isolated, it is probable that the departure of the second benzotriazole and the subsequent cyclization are faster than the initial homoallyl formation. Grieco [86JA3512] suggested that the final step from intermediate **2.7** (Scheme 2.2) was a concerted olefin-iminium cyclization.



2.1	R^1
a	$PhCH_2$
b	PhCHMe
c	$PhCH_2CH_2$

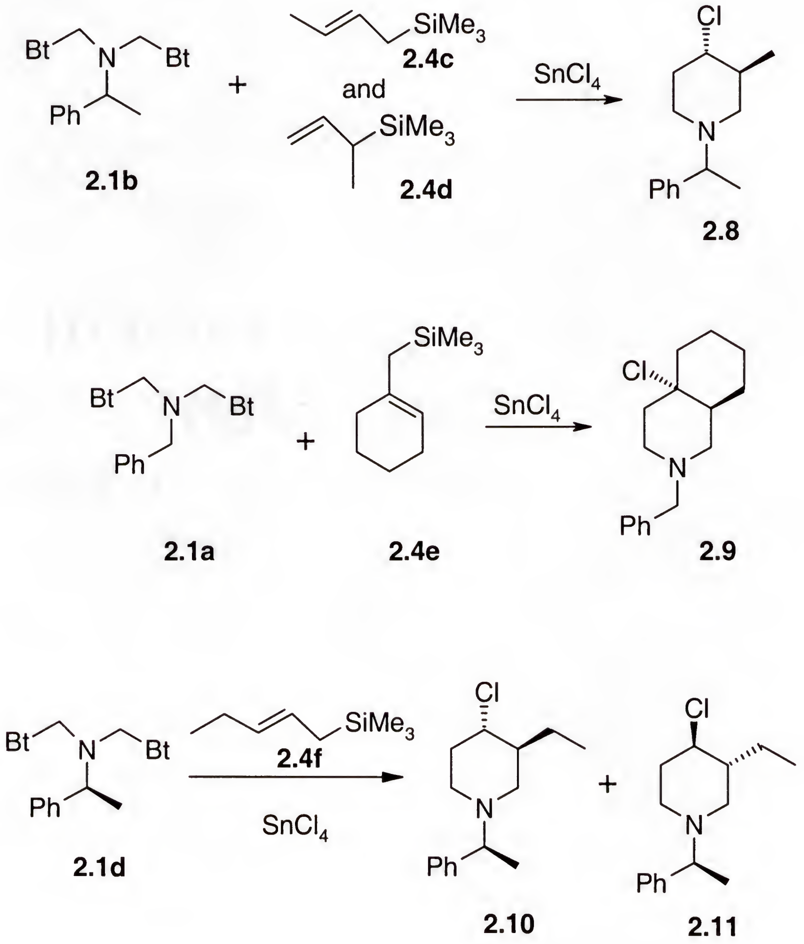
2.4	R^2
a	H
b	Me

	R^1	R^2	2.2	2.5
a	$PhCH_2$	H	62%	
b	$PhCH_2$	Me	68%	16%
c	PhCHMe	H	58%	
d	PhCHMe	Me	68%	21%
e	$PhCH_2CH_2$	H	64%	



Scheme 2.2

Additional substituted allyltrimethylsilanes can be used in this reaction (Scheme 2.3). The mixture of crotyltrimethylsilane **2.4c** and 1-methylallyltrimethylsilane **2.4d** (prepared according to the literature [48JA2872]) reacted with **2.1b** under the same conditions to give the 1,3,4-trisubstituted piperidine **2.8**. Cyclic allylsilane **2.4e** (prepared according to the literature [80TL3915]) afforded the bicyclic amine **2.9**. By analogy with the literature reports [86JA3512, 87JCS(CC)185], we locate the chloride *trans* to the alkyl substituent in compounds **2.8** and **2.9**.



Scheme 2.3

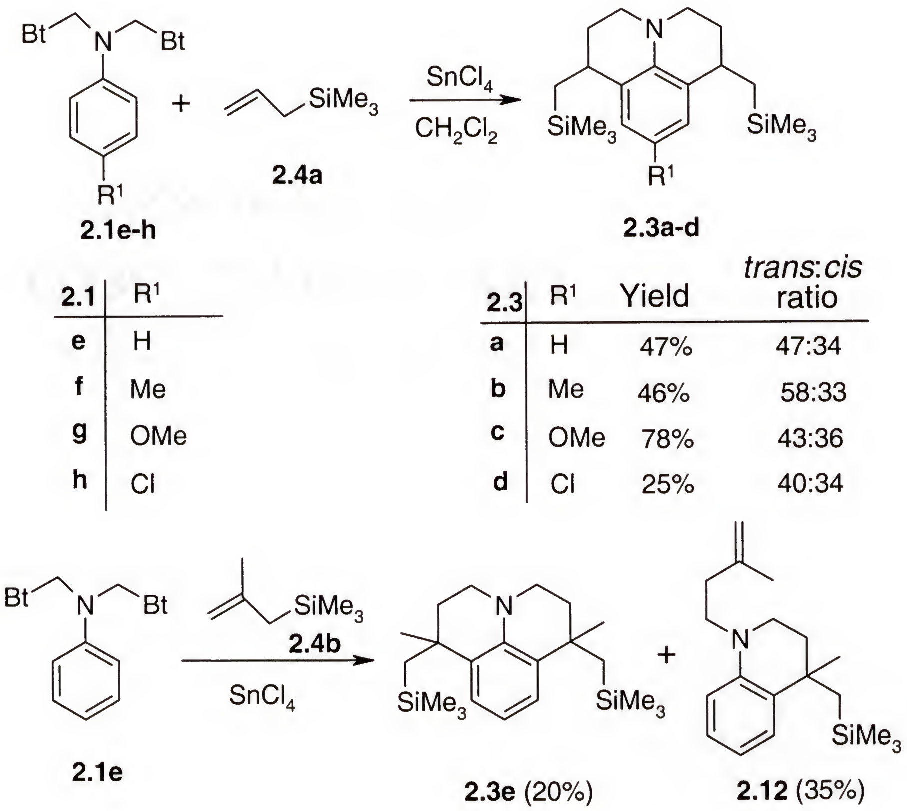
Chiral piperidines can be prepared from chiral starting amines. Chiral (L) **2.1d** (analogous to racemic compound **2.1b**) reacted with trimethyl[(E)-2-pentenyl]silane **2.4f** to give **2.10** and **2.11** in 58% yield; however, the mixture could not be separated by a silica gel column. Based on their NMR spectra, the ratio of **2.10**:**2.11** was about 60:40 as measured from the -CH_3 group integrals.

Thus, starting from readily available **2.1**, we prepared 4-chloropiperidines **2.2a-e** *via* a [3+3] cycloaddition in mild reaction conditions while avoiding the use of trifluoroacetic acid. 4-Chloropiperidines **2.2a-e** are useful building blocks for many biologically active compounds, *e.g.* antihistaminic *N*-heterocyclic 4-piperidinamines [85JMC1925] and fentanyl analogues [84JMC1570, 83JMC1747].

Reaction of *N,N*-Bis[(benzotriazol-1-yl)methyl]anilines **2.1** with Allyltrimethylsilanes to Give Trimethylsilyl Julolidines **2.3.** Substituted julolidines were prepared by our group *via* the reaction of *N,N*-bis[(benzotriazol-1-yl)methyl]aniline (**2.1**) (R = Ph) with electron-rich alkenes, *e.g.* *N*-vinyl-2-pyrrolidinone, ethyl vinyl ether and enolizable aldehydes [96JOC3117]. In a previous paper, we reported that allyltrimethylsilanes reacted with the iminium ions derived from *N*-(benzotriazol-1-yl)methylanilines to give tetrahydroquinolin-4-yl silanes [99JHC371]. Under similar conditions, reactions of *N,N*-bis[(benzotriazol-1-yl)methyl]anilines **2.1** with allyltrimethyl-silanes **2.4** now yield 1,7,9-trisubstituted trimethylsilyl julolidines **2.3a-d** for which the isolated yields and *trans*:*cis* ratios (from GC/MS) are indicated in Scheme 2.4.

The ^{13}C NMR spectra of the crude products **2.3** indicated a mixture of *cis* and *trans* isomers, though ^{1}H NMR spectra were identical. The predominant isomer was isolated by silica gel chromatography, and assigned as *trans*-geometry by comparing the ^{13}C NMR spectra to the literature [96JOC3117]. The reaction of **2.1e** with 2-

methylallyltrimethylsilane (**2.4b**) gave an inseparable *cis*, *trans* mixture of julolidine **2.3e** (yield 20%), along with the desilylation product **2.12** (35% yield).



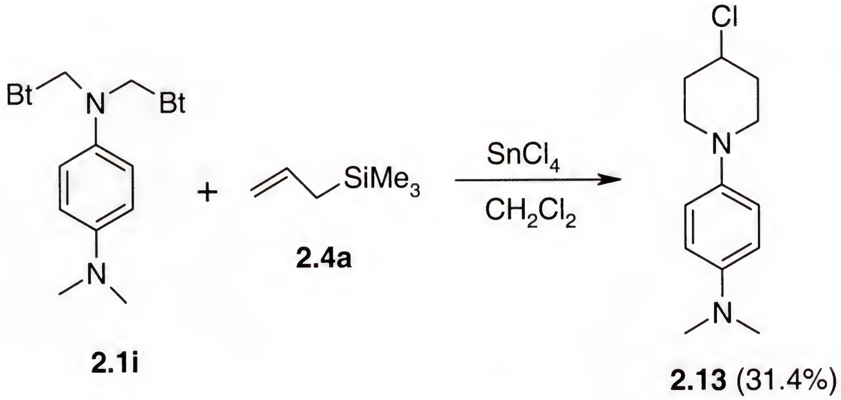
2.1	R^1
e	H
f	Me
g	OMe
h	Cl

2.3	R^1	Yield	*trans:cis* ratio
a	H	47%	47:34
b	Me	46%	58:33
c	OMe	78%	43:36
d	Cl	25%	40:34

Scheme 2.4

As shown in Scheme 2.4, *para* electron-releasing substituents (CH_3, OCH_3) on the aniline favored the formation of the julolidine product **2.3**, whereas electron-withdrawing substituents (Cl) led to **2.3** in low yield. This can be explained by the ease of electrophilic attack on the electron-rich *ortho* position of the aromatic ring that bears a *para* electron-releasing group. There were no significant effects from the *para* substituents on the ratios of *trans:cis* products, which were 1:1 to 1.5:1 in all the entries.

A somewhat surprising result occurred when R^1 was the strongest electron-releasing group -N(Me)$_2$; 4-chloropiperidine **2.13** was obtained instead of the julolidine (Scheme 2.5). Possibly because $SnCl_4$ could coordinate strongly with the nitrogen atom of -N(CH$_3$)$_2$ group which significantly reduced the electron density of aromatic ring, electrophilic cyclization of carbocation intermediate onto the aromatic ring did not occur. Instead, **2.1i** acted as a 1,3-dication synthon and was trapped by allyltrimethylsilane (a 1,3-dianion equivalent) to form the piperidine ring through a [3+3] cycloaddition reaction.



Scheme 2.5

2.3 Conclusion

In summary, piperidine derivatives **2.2** and trimethylsilyl julolidines **2.3** were prepared from the same synthons, *N,N*-bis[(benzotriazol-1-yl)methyl]amino derivatives **2.1**. Reactions of *N,N*-bis[(benzotriazol-1-yl)methyl]benzylamines and *N,N*-bis[(benzotriazol-1-yl)methyl](*p*-*N',N'*-dimethyl phenyl)amine with allyltrimethylsilanes yielded substituted piperidines **2.2**. Other *N,N*-bis[(benzotriazol-1-yl)methyl]anilines (unsubstituted and *p*-CH$_3$, OCH$_3$, Cl) gave access to julolidine analogues.

2.4 Experimental Section

General Comments. The NMR spectra were recorded with tetramethylsilane as the internal reference for ^{1}H (300 MHz) or solvent as the internal reference for ^{13}C (75 MHz). See literature for the preparation and characterization of *N,N*-bis[(benzotriazol-1-yl)methyl]amines: for **2.1a** and **2.1c** [87JCS(P1)799], for **2.1b** and **2.1d** [98H2535], for **2.1e-i** [90CJC446].

General Procedure for the Reaction of **2.1** with Allyltrimethylsilanes. Allyltrimethylsilane (3 mmol) was added to a solution of **2.1** (1 mmol) in dry CH_2Cl_2 (20 mL) being cooled by an ice-water bath. $SnCl_4$ (1 mmol) was then added to the stirred mixture. The resulting mixture was kept at this temperature for 2 h and then allowed to warm to room temperature overnight. A NaOH solution (2N, 20 mL) was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude products, which were further purified by silica gel column chromatography to give the pure products.

1-Benzyl-4-chloropiperidine (**2.2a**) [86JA3512].

2.1a reacted with **2.4a**. Yield 62%. ^{1}H NMR δ 1.95-2.09 (m, 2H), 2.11-2.26 (m, 2H), 2.26-2.42 (m, 2H), 2.78-2.90 (m, 2H), 3.62 (s, 2H), 4.20-4.09 (m, 1H), 7.35-7.44 (m, 5H); ^{13}C NMR δ 35.6, 51.3, 57.5, 62.9, 127.1, 128.2, 129.0, 138.3. MS (*m/z*): 209 (M^+, 10), 174 (M-Cl, 50), 91 (100).

1-Benzyl-4-chloro-4-methylpiperidine (**2.2b**).

2.1a reacted with **2.4b** to give **2.2b** and **2.5b**. **2.2b** Yield 68%. ^{1}H NMR δ 1.62 (s, 3H), 1.77-2.48 (m, 4H), 2.45 (t, *J* = 11.0 Hz, 2H), 2.60-2.72 (m, 2H), 3.54 (s, 2H), 7.20-7.32 (m, 5H); ^{13}C NMR δ 39.2, 40.8, 49.6, 63.0, 69.8, 127.0, 128.2, 129.1, 138.5. Anal. Calcd for $C_{13}H_{18}ClN$: C, 69.78; H, 8.13; N, 6.26. Found: C, 69.58; H, 8.32; N, 6.47.

1-Benzyl-4-methylenepiperidine (**2.5b**).

Yield 16%. If quenched with dry methanol instead of 2N NaOH solution, the yield of **2.5b** was 5%. ^{1}H NMR δ 2.38-2.49 (m, 4H), 2.57-2.70 (m, 4H), 3.70 (s, 2H), 4.83 (s, 2H), 7.36-7.52 (m, 5H); ^{13}C NMR δ 34.6, 55.0, 62.9, 107.6, 126.9, 128.1, 129.1, 138.6, 146.7. HRMS Calcd for $C_{13}H_{17}N$: 188.1439 (M+1). Found: 188.1437 (M+1).

1-(1-Phenylethyl)-4-chloropiperidine (**2.2c**).

2.1b reacted with **2.4a** to give **2.2c**. Yield 58%. ^{1}H NMR δ 1.38 (d, *J* = 6.7 Hz, 3H), 1.82-1.99 (m, 2H), 1.99-2.15 (m, 2H), 2.15-2.28 (m, 2H), 2.69-2.79 (m, 1H), 2.80-2.91 (m, 1H), 3.45 (q, *J* = 6.7 Hz, 1H), 3.92-4.15 (m, 1H), 7.24-7.33 (m, 5H); ^{13}C NMR δ 19.4, 35.9, 48.6, 57.8, 64.4, 126.9, 127.5, 128.2, 143.9. Anal. Calcd for $C_{13}H_{18}ClN$: C, 69.78; H, 8.13; N, 6.26. Found: C, 69.75; H, 8.35; N, 6.56.

1-(1-Phenylethyl)-4-chloro-4-methylpiperidine (**2.2d**).

2.1b reacted with **2.4b** to give **2.2d** and **2.5d**. **2.5d** Yield 68%. ^{1}H NMR δ 1.60 (d, *J* = 6.8 Hz, 3H), 1.83 (s, 3H), 1.94-2.20 (m, 4H), 2.58-2.70 (m, 2H), 2.72-2.85 (m, 1H), 3.00-3.11 (m, 1H), 3.68 (q, *J* = 6.8 Hz, 1H), 7.43-7.55 (m, 5H); ^{13}C NMR δ 19.5, 33.1, 41.1, 47.3 [46.3], 64.6, 70.0, 126.8, 127.5, 128.2, 144.3. Anal. Calcd for $C_{14}H_{20}ClN$: C, 70.71; H, 8.50; N, 5.89. Found: C, 70.73; H, 8.72; N, 6.23.

1-(1-Phenylethyl)-4-methylenepiperidine (**2.5d**).

Yield 21%. ^{1}H NMR δ 1.55 (d, J = 6.8Hz, 3H), 2.30-2.42 (m, 4H), 2.52-2.68 (m, 4H), 3.65 (q, J = 6.7 Hz, 1H), 4.77 (s, 2H), 7.32-7.50 (m, 5H); ^{13}C NMR δ 19.3, 34.8, 52.0, 64.2, 107.1, 126.7, 127.6, 128.1, 143.8, 147.0. Anal. Calcd for $C_{14}H_{19}N$: N, 6.96. Found: N, 7.15.

1-Phenethyl-4-chloropiperidine (**2.2e**).

2.1c reacted with **2.4a** to give **2.2e**. Yield 64%. ^{1}H NMR δ 2.04-2.20 (m, 2H), 2.20-2.39 (m, 2H), 2.39-2.58 (m, 2H), 2.70-2.82 (m, 2H), 2.88-3.09 (m, 4H), 4.16-4.32 (m, 1H), 7.30-7.50 (m, 5H); ^{13}C NMR δ 33.8, 35.5, 51.2, 57.3, 60.3, 126.0, 128.4, 128.6, 140.2. Anal. Calcd for $C_{13}H_{18}ClN$: C, 69.78; H, 8.13; N, 6.26. Found: C, 69.62; H, 8.37; N, 6.36.

1-(1-Phenylethyl)-3-methyl-4-chloropiperidine (**2.8**).

2.1b reacted with the mixture of **2.4c** and **2.4d** [48JACS2872] to give **2.8**. Yield 42%. ^{1}H NMR δ 0.98 (d, J = 6.3 Hz, 3H) [1.06 (d, J = 6.3 Hz, 3H)], 1.37 (d, J = 3.6 Hz, 3H) [1.39 (d, J = 3.5 Hz, 3H)], 1.60-2.20 (m, 5H), 2.78-2.88 (m, 1H), 2.96-3.08 (m, 1H), 3.38-3.50 (m, 2H), 7.20-7.39 (m, 5H); ^{13}C NMR δ 17.2 [17.3], 19.4, 36.7 [36.6], 40.1, 50.1 [50.4], 57.3 [57.6], 64.0 [63.9], 65.5 [65.4], 126.9, 127.5, 128.2, 143.6. Anal. Calcd for $C_{14}H_{20}ClN$: N, 5.89. Found: N, 6.07.

2-Benzyl-4a-chlorodecahydroisoquinoline (**2.9**).

2.1a reacted with **2.4e** [80TL3915] to give **2.9**. Yield 36%. ^{1}H NMR δ 1.18-1.26 (m, 2H), 1.26-1.72 (m, 5H), 1.72-1.98 (m, 4H), 2.09 (t, J = 11.0 Hz, 1H), 2.43 (dd, J =

2.7, 11.0 Hz, 1H), 2.55 (td, *J* = 4.2, 11.0 Hz, 1H), 2.71 (d, *J* = 11.0 Hz, 1H), 3.48 (s, 2H), 7.15-7.27 (m, 5H).; ^{13}C NMR δ 21.7, 25.4, 25.7, 40.9, 41.1, 45.2, 49.4, 54.9, 63.0, 76.6, 127.0, 128.2, 129.1, 138.5. HRMS Calcd for $C_{16}H_{22}ClN$: 264.1519 (M+1). Found: 264.1504 (M+1).

1-[(1*S*)-1-Phenylethyl]-3-ethyl-4-chloropiperidine (**2.10**).

2.1d reacted with **2.4f** to give **2.10** and **2.11** (in the bracket). Yield 58%. ^{1}H NMR δ 0.90 (t, *J* = 7.5 Hz, 3H) [0.81 (t, *J* = 7.5 Hz, 3H)], 1.36 (d, *J* = 5.4 Hz, 3H) [1.38 (d, *J* = 6.6 Hz, 3H)], 1.60-1.80 (m, 3H), 1.85-2.20 (m, 4H), 2.72-3.14 (m, 2H), 3.40-3.50 (m, 1H), 3.50-3.63 (m, 1H), 7.20-7.38 (m, 5H); ^{13}C NMR δ 10.9[10.8], 19.7[18.9], 24.0[23.8], 36.3[36.2], 45.9, 49.7[49.8], 54.3[54.2], 63.9[63.7], 64.3, 126.8[126.9], 127.4[127.5], 128.2, 143.5. Anal. Calcd for $C_{15}H_{22}ClN$: C, 71.54; H, 8.82; N, 5.56. Found: C, 71.26; H, 9.20; N, 5.74.

1,7-Bis[(trimethylsilyl)methyl]-2,3,6,7-tetrahydro-*1H,5H*-pyrido[3,2,1-*ij*] quinoline (**2.3a**).

2.1e reacted with **2.4a** to give **2.3a**. Yield 47%. ^{1}H NMR δ: 0.20 (s, 18H), 1.01 (dd, *J* = 10.2, 14.8 Hz, 2H), 1.14 (dd, *J* = 4.2, 14.9 Hz, 2H), 1.85-1.91 (m, 2H), 2.05-2.20 (m, 2H), 3.04-3.09 (m, 2H), 3.20-3.27 (m, 2H), 3.34-3.41 (m, 2H), 6.65-6.68 (m, 1H), 6.97 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR δ: -0.6, 25.3, 28.9, 32.7, 46.5, 115.2, 125.9, 128.4, 140.6. MS (*m/z*): 345 (M^+, 50), 258 (100). Anal. Calcd for $C_{20}H_{35}NSi_2$: N, 4.05. Found: N, 4.20.

9-Methyl-1,7-bis[(trimethylsilyl)methyl]-2,3,6,7-tetrahydro-*1H,5H*-pyrido [3,2,1-*ij*]quinoline (**2.3b**).

2.1f reacted with **2.4a** to give **2.3b**. Yield 46%. ^{1}H NMR δ 0.20 (s, 18H), 1.00 (dd, *J* = 10.5, 14.8 Hz, 2H), 1.15 (dd, *J* = 4.0, 11.0 Hz, 2H), 1.83-1.87 (m, 2H), 2.08-2.23 (m, 2H), 2.33 (s, 3H), 2.97-3.09 (m, 2H), 3.09-3.22 (m, 2H), 3.24-3.33 (m, 2H), 6.80 (s, 2H); ^{13}C NMR δ -0.6, 20.5, 25.7, 29.3, 32.7, 46.9, 126.5, 126.6, 128.8, 138.2. MS (*m/z*): 359 (M$^+$, 80), 272 (100). Anal. Calcd for $C_{21}H_{37}NSi_2$: C, 70.11; H, 10.39; N, 3.89. Found: C, 69.96; H, 10.26; N, 4.26.

9-Methoxy-1,7-bis[(trimethylsilyl)methyl]-2,3,6,7-tetrahydro-*1H,5H*-pyrido [3,2,1-*ij*] quinoline (**2.3c**).

2.1g reacted with **2.4a** to give **2.3c**. Yield 78%. ^{1}H NMR δ 0.20 (s, 18H), 1.02 (dd, *J* = 10.5, 14.9 Hz, 2H), 1.17 (dd, *J* = 3.8, 14.9 Hz, 2H), 1.78-1.90 (m, 2H), 2.10-2.22 (m, 2H), 2.98-3.07 (m, 2H), 3.07-3.17 (m, 2H), 3.20-3.29 (m, 2H), 3.88 (s, 3H), 6.62 (s, 2H); ^{13}C NMR δ -0.6, 25.8, 29.6, 33.0, 47.3, 55.8, 112.0, 130.3, 135.8, 150.7. MS (*m/z*): 375 (M$^+$, 100), 360 (40), 288 (90). Anal. Calcd for $C_{21}H_{37}NOSi_2$: N, 3.73. Found: N, 3.91.

9-Chloro-1,7-bis[(trimethylsilyl)methyl]-2,3,6,7-tetrahydro-*1H,5H*-pyrido [3,2,1-*ij*] quinoline (**2.3d**).

2.1h reacted with **2.4a** to give **2.3d**. Yield 25%. ^{1}H NMR δ 0.20 (s, 18H), 0.97 (dd, *J* = 10.4, 14.8 Hz, 2H), 1.10 (dd, *J* = 4.1, 15.0 Hz, 2H), 1.75-1.87 (m, 2H), 2.08-2.16 (m, 2H), 2.96-3.01 (m, 2H), 3.16-3.22 (m, 2H), 3.31-3.39 (m, 2H), 6.91 (s, 2H); ^{13}C

NMR δ -0.6, 25.1, 28.6, 32.9, 46.4, 119.6, 125.4, 130.0, 139.1. MS (*m/z*): 379 (M^+, 90), 292 (100). Anal. Calcd for $C_{20}H_{34}NClSi_2$: C, 63.19; H, 9.03; N, 3.69. Found: C, 63.47; H, 9.10; N, 3.71.

1,7-Dimethyl-1,7-bis[(trimethylsilyl)methyl]-2,3,6,7-tetrahydro-*1H,5H*-pyrido [3,2,1-*ij*] quinoline (**2.3e**).

2.1e reacted with **2.4b** to give **2.3e** (20%) and **2.12** (35%). ^{1}H NMR δ 0.17 (s, 9H), 0.20 (s, 9H), 1.37 (dd, *J* = 5.5, 14.8 Hz, 2H), 1.48 (dd, *J* = 11.8, 16.6 Hz, 2H), 1.62 (s, 3H), 1.63 (s, 3H), 1.95-2.10 (m, 2H), 2.23-2.31 (m, 2H), 3.32-3.46 (m, 4H), 6.82-6.90 (m, 1H), 7.22-7.31 (m, 2H); ^{13}C NMR δ 33.2[32.1], 33.9[33.3], 35.2[35.1], 36.8[36.7], 47.1[46.9], 115.3[115.4], 123.8, 124.3, 131.8. MS (*m/z*): 373 (M^+, 60), 358 (40), 286 (100). Anal. Calcd for $C_{22}H_{39}NSi_2$: C, 70.70; H, 11.54; N, 3.75. Found: C, 71.02; H, 11.13; N, 4.01.

1-(3-Methyl-3-butenyl)-4-[(trimethylsilyl)methyl]-1,2,3,4-tetrahydroquinoline (**2.12**).

^{1}H NMR δ 0.22 (s, 9H), 1.35, 1.42 (AB, *J* = 14.8 Hz, 2H), 1.62 (s, 3H), 2.09 (s, 3H), 1.95-2.20 (m, 2H), 2.50-2.62 (m, 2H), 3.58 (t, *J* = 6.0 Hz, 2H), 3.69 (t, *J* = 7.7 Hz, 2H), 5.04 (s, 1H), 5.08 (s, 1H), 6.82-6.90 (m, 2H), 7.26-7.34 (m, 1H), 7.46 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 0.8, 22.8, 32.0, 32.4, 33.7, 34.8, 36.8, 45.6, 50.1, 110.5, 111.4, 115.3, 126.1, 126.7, 132.6, 143.4, 143.9. Anal. Calcd for $C_{19}H_{31}NSi$: N, 4.65. Found: N, 4.69.

N-[4-(4-Chloropiperidino)phenyl]-*N,N*-dimethylamine (**2.13**).

2.1i reacted with **2.4a** to give **2.13.** Yield 31%. M. P. 70.0-72.0 °C. ^{1}H NMR δ 2.12-2.26 (m, 2H), 2.30-2.44 (m, 2H), 3.03 (s, 6H), 3.03-3.10 (m, 2H), 3.45-3.58 (m, 2H), 4.25-4.36 (m, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR δ 35.5, 41.5, 49.4, 57.3, 114.4, 119.0, 142.9, 145.9. HRMS Calcd for $C_{13}H_{19}ClN_2$: 238.1236. Found: 238.1139.

CHAPTER 3

PREPARATION OF POLYSUBSTITUTED PIPERIDINES *VIA* RADICAL CYCLIZATION

3.1 Introduction

Radical cyclizations are frequently used for ring construction, especially for 5-membered rings [91COC(4)779, 95MI2, 95COG(1)336, 91CR1237, 96OR301], such as cyclopentanes, tetrahydrofurans and pyrrolidines [98TL2429, 99JOC3335, 96JA4059, 97JOC1125, 88TL6685, 85JOC5620]. However, radical cyclizations leading to 6-membered rings are less common than those leading to 5-membered rings due to (i) slower cyclization rates, (ii) lower regioselectivity of 6-exo radical cyclization compared with 5-exo cyclization and (iii) competitive 1,5-hydrogen transfer [91COC(4)779, 95MI2, 95COG(1)336, 91CR1237, 96OR301, 88JA5900, 93JA6051].

Mariano *et al.* reported that photo-induced radical cyclizations of α-silylaminoenones and α-silylynones furnished functionalized piperidines and piperidine derivatives [94TL999, 96T3195], and used SET-photo-induced α-aminoalkyl radical cyclizations to prepare indolizidines and quinolizidines [94TL8319]. Aurrecoechea *et al.* synthesized six-membered rings by cyclization of α-aminoalkyl radicals [97JOC1125]. However, these previous 6-exo radical cyclization reactions require an activating electron-withdrawing group on the alkene terminus.

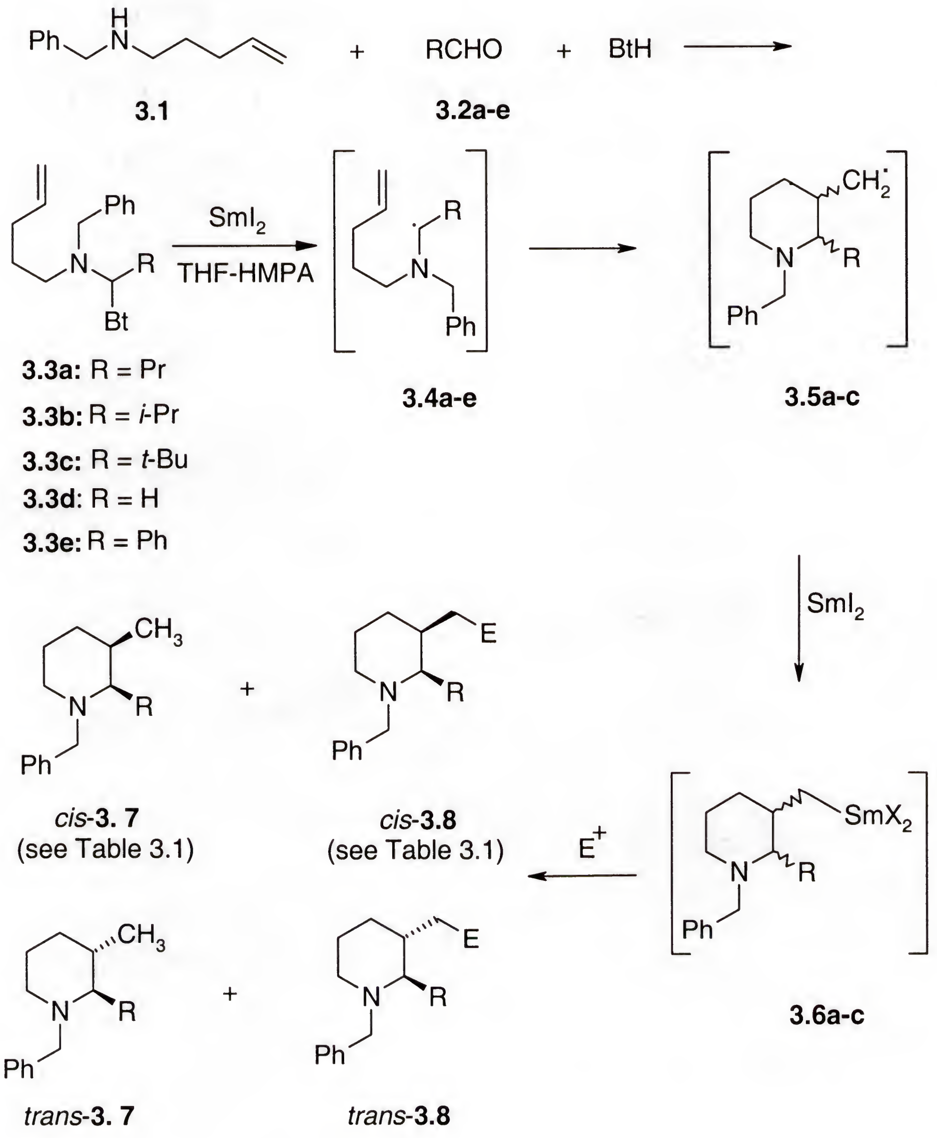
Molander *et al.* prepared six-membered carbocyclic and some heterocyclic rings by radical cyclization of phenyl or ketyl-olefin radicals to unactivated double bonds promoted by samarium diiodide [90JOC6171, 92JOC3132, 95JOC872]. However, no nitrogen-heterocycles were reported by this method. Parsons and Pettifer demonstrated that substituted pyrrolidines and piperidines could be formed using tin hydride-mediated cyclization of a variety of α- and β-homoallylamino aldehydes [98JCS(P1)651]. Pandey *et al.* reported that photo-induced electron transfer promoted intramolecular cyclizations of α-silylmethyl amines to unactivated double bonds could afford nitrogen-containing six-membered ring [94T8185, 96JCS(P1)219]. Jones *et al.* effected aryl-radical cyclizations to unactivated double bonds to prepare quinolines, isoquinolones and 1-benzazepin-2-ones by treatment of appropriate *o*-substituted aryl halides with tri-*n*-butyltin hydride [91TL2829]. We previously achieved regioselective additions of α-aminoalkyl radicals to unactivated double bonds to give pyrrolidines [99JOC3335], and have now extended this approach to 6-exo-α-aminoalkyl radical cycloadditions affording polysubstituted piperidines.

3.2 Results and Discussion

The Preparation of Benzotriazole Derivatives **3.3a-e**. Starting materials **3.3a-e** were prepared by the condensation of a secondary amine **3.1** [91T2005], aldehydes **3.2a-e** and benzotriazole in the presence of molecular sieves in Et_2O at room temperature (Scheme 3.1). Compounds **3.3a-e** decompose easily in contact with water and this decomposition is accelerated by silica gel. Compound **3.3e** is crystalline and was purified by recrystallization from dry diethyl ether. Benzotriazole derivatives **3.3a-d** could not be purified, but can be used in a crude form for preparative purposes. These crude products, **3.3a-d**, contained *ca* 3% of secondary amine **3.1** as a contaminant as demonstrated by a singlet around 3.8 ppm which was assigned to the methylene $PhCH_2N$ of **3.1** in the crude

^{1}H NMR spectra. Structures **3.3a-d** were supported by AB systems around 3.0-4.5 ppm in their ^{1}H NMR spectra for the *PhCH$_2$N* methylene and by the correct integration ratio of this signal to that characteristic of the benzotriazole ring protons [97JOC1125].

Cyclization Reactions of **3.3a-e.** Initial cyclization studies were conducted on benzotriazole derivative **3.3a**. Treatment of **3.3a** with samarium diiodide in THF-HMPA under argon at 0 °C, followed by a water quench gave piperidine derivative **3.7a** as a



Scheme 3.1

Table 3.1. The Preparation of Piperidine Derivatives **3.7** and **3.8**.

SM	Electrophile	Product **3.8**					Product **3.7**			
		No	R	E	Yield	Ratio*	No	R	Yield	Ratio [a]
3.3a	H_2O	[b]					**a**	Pr	56	1/8.9
3.3a	EtCOEt	**a**	Pr	EtC(OH)Et	51	1/4.3	**a**	Pr	34	1/1.1
3.3a	MeCOEt	**b**	Pr	MeC(OH)Et	43	1/7.5	**a**	Pr	30	1/1.2
3.3a	MeCOPr	**c**	Pr	MeC(OH)Pr	41	1/4.8	**a**	Pr	33	1/1.1
3.3a	PhCHO	**d**	Pr	PhCHOH	17	1/3.2	**a**	Pr	47	1/1.2
3.3a	MeCHO	**e**	Pr	MeCHOH	21	1/6.4	**a**	Pr	49	1/1.1
3.3a	*i*-PrNCO	**f**	Pr	*i*-PrNHCO	25	1/2.5	**a**	Pr	50	1/1.3
3.3b	H_2O	[b]					**b**	*i*-Pr	53	1/1.4
3.3c	H_2O	[b]					**c**	*t*-Bu	52	1/1.1

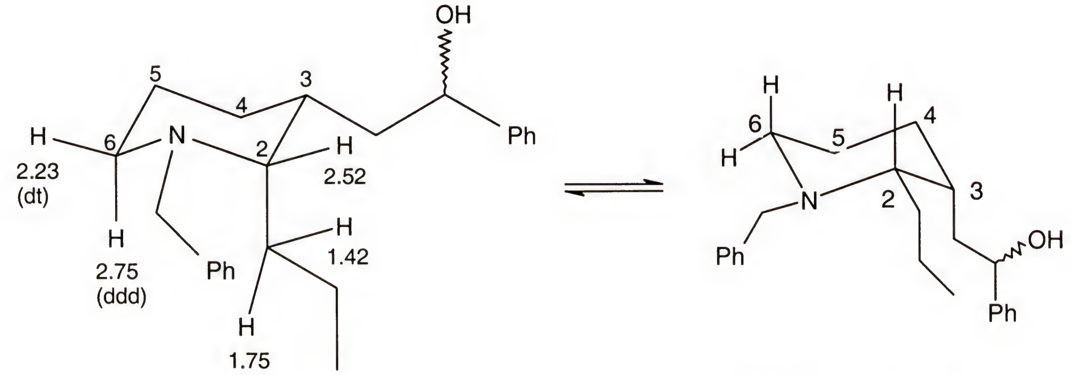
[a] This is the *trans*/*cis* ratio and were determined by GC/MS.
[b] In these runs no electrophile was added.

mixture of *cis* and *trans* isomers in 56% yield. This reaction is thought to proceed *via* radical intermediates **3.4a** and **3.5a**, and organic samarium derivative **3.6a** [99JOC3335] (Scheme 3.1). The *cis* and *trans* ratios of **3.7a** (Table 3.1) were determined by GC/MS results.

When a ketone (3-pentanone, 2-butanone or 2-pentanone) was added as electrophile to the reaction mixture of **3.3a** and SmI_2, intermediate **3.6a** was trapped to form piperidines **3.8a-c** in 41-51% yields, together with the protonated product **3.7a,** in 30-34% yield, as a by-product. Changing the solvent from THF to THP, or extending the reaction time to four days before quenching the reaction by water when compound **3.3a** was used as starting material and 3-pentanone was used as electrophile did not decrease the yield of protonated product **3.7a**.

When benzaldehyde, acetaldehyde or isopropyl isocyanate were used as electrophiles, **3.7a** was obtained as the major product in 47-50% yield, along with compounds **3.8d-f** formed by trapping **3.6a** with the corresponding electrophile in 17-25% yield. Compounds *cis*-**3.8b-e**, which possess an additional extra-cyclic asymmetric center, were isolated as mixture of diastereomers. The NMR spectra of the diastereomers of *cis*-**3.8b-e** show only small differences.

The structural integrity and the stereochemistry of compound *cis*-**3.8d** was investigated by NMR. The proton spectrum of *cis*-**3.8d** at room temperature displayed broad lines, indicative of slowed exchange between conformations (see Figure 3.1). At 55 °C the exchange was fast and sharp lines allowed the measurement of the coupling constants. The complete assignments of the ^{1}H and ^{13}C chemical shifts were made using DQCOSY and the gradient HMQC spectra. The coupling constants of the two protons in position 6 (2.75 ppm, *ddd*, 12.9, 9.1, 3.3 Hz and 2.23 ppm, *dt*, 12.9, 4.7 Hz) indicated that in the preferred conformation of the proton at 2.75 is axial. The NOESY spectrum contained two sets of cross-peaks: (i) between the protons at 2.23 and 2.52 and (ii) between those at 2.75 and 1.75. We believe cross peaks (i) arise from the minor conformer of *cis*-**3.8d** (see Figure 3.1), whereas cross peaks (ii) arise from the major conformer of *cis*-**3.8d**. In the preferred conformation, the propyl group in position 2 is axial, because it is *cis* to the axial proton in position 6. We assign the substituent in position 3 of *cis*-**3.8d** as *cis* to the 2-propyl group because if in positions 2 and 3 were mutually *trans*, they would both be axial in their most stable conformation, which is highly unlikely. By analogy, we assigned all the major products **3.7a** and **3.8a-f** as *cis* isomers. We also examined the ^{1}H-spectra of *cis*-**3.8d** at low temperature. Coalescence occurred at *ca* –20 °C and the spectra were sharp again at – 80 °C. The easiest pattern to interpret was the benzyl -CH_2 signal which changed from an AB system at high temperature to an AX system at low temperature. A detailed interpretation of the spectra was not possible because of their complexity.



cis-**3.8d** (major conformer)

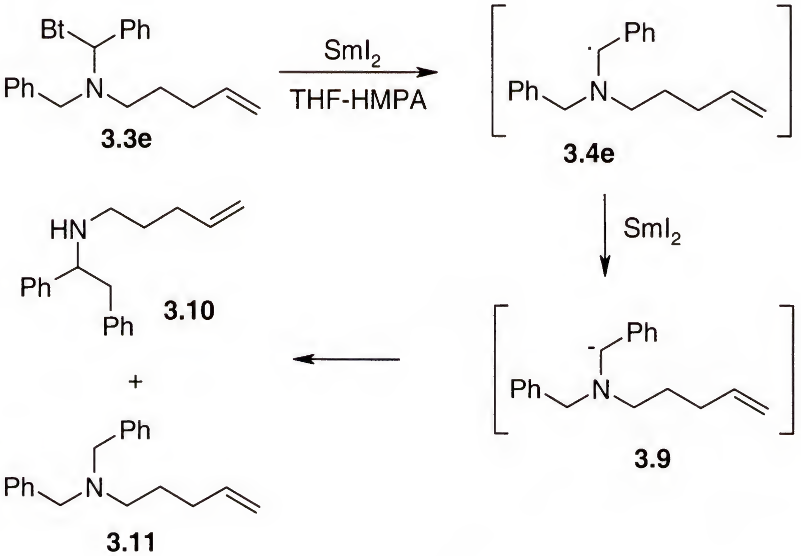
cis-**3.8d** (minor conformer)

Figure 3.1

We next used compounds **3.3b** and **3.3c** which cyclized to produce **3.7b** and **3.7c** with the larger *i*-propyl and *t*-butyl groups at the C-2 position. After quenching by water, cyclization product **3.7b** was obtained in 51% yield. Compound **3.7c** (yield estimated as 52% by GC/MS) was isolated only as a mixture with an acyclic product arising from the protonation of intermediate **3.4c**.

Attempted use of **3.3d** (i. e. R = H), as starting material failed. Reaction of **3.3d** with SmI_2 and quenched by water gave a complex mixture in which no cyclic product was detected. The primary radical **3.4a** is presumably too short-lived to cyclize. The yields of compounds **3.8** and **3.7** in Table 3.1 are all based on the amount of starting amine **3.1** used, and are, therefore, overall yields for a two-pot, three-step reaction process. The total yields for **3.8a-f** were more than 70% when the amount of **3.7a** was taken into account, which indicates that the radical cyclization proceeds smoothly.

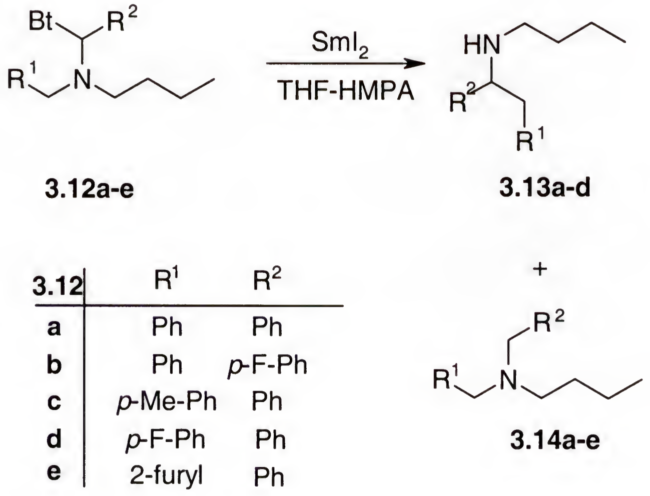
The [1,2]-aza-Wittig Rearrangement Reaction of **3.11a-f.** When compound **3.3e** was reacted with SmI_2 and the reaction mixture quenched by water, no cyclic products of type **3.7** and **3.8** were found, instead compounds **3.10** and **3.11** were obtained (Scheme 3.2). We believe that the major product **3.10** is formed by a [1,2]-aza-Wittig rearrangement of α-aminocarbanion **3.9**, and that another portion of **3.9** undergoes protonation to **3.11**. The structure of compounds **3.10** and **3.11** were supported by their ^{1}H NMR spectra. The double doublets around 4.8 ppm with J = 10.6 Hz and 1.5 Hz and the multiplets around 5.7 ppm showed the existence of a terminal double bond in compounds **3.10** and **3.11**. The singlet at 3.56 ppm with four protons in the ^{1}H NMR spectrum of compound **3.11** which was assigned to the two *PhCH₂N* methylene demons-



Scheme 3.2

trated that these two *PhCH*$_2$ group were attached to *N* respectively. However, this singlet was not found in the ^{1}H NMR spectrum of compound **3.10**. Instead, one doublet around 2.9 ppm with two protons and one triplet around 3.8 ppm with one proton were found. These supported the structure of compound **3.10** and showed that the rearrangement had occurred. The different reaction course is probably due to radical **3.4e** being more stable (and less reactive) so that it is reduced further to carbanion **3.9** before cyclization occurs.

We further explored this rearrangement reaction using **3.12a-e** (Scheme 3.3) as starting materials to ascertain its scope and limitations. Benzotriazole derivatives **3.12a-e** were prepared using the same method as for the preparation of compounds **3.3a-e**. Compounds **3.12a-e** are crystalline. They were purified by recrystallization from diethyl ether and their structures were supported by NMR spectra and microanalysis or HRMS. Treatment of **3.12a-d** with samarium diiodide in THF/HMPA under argon at 0 °C, followed by a water quench, gave mixtures of the corresponding rearrangement **3.13a-d** and reduction products **3.14a-d** in which **3.13a-d** predominated (Table 3.2). When **3.12e**



3.12a-e

3.13a-d

3.14a-e

3.12	R^1	R^2
a	Ph	Ph
b	Ph	*p*-F-Ph
c	*p*-Me-Ph	Ph
d	*p*-F-Ph	Ph
e	2-furyl	Ph

Scheme 3.3

Table 3.2. The Yields (%) of Compounds **3.13a-d** and **3.14a-e**.‡

Entry	R^1	R^2	**3.13**	**3.14**
a	Ph	Ph	40	27
b	Ph	p-F-C_6H_4	60	23
c	p-Me-C_6H_4	Ph	60	29
d	p-F-C_6H_4	Ph	57	35
e	2-Furyl	Ph	0	100

‡ All the yields is from GC/MS results.

was used as starting material to perform this reaction, only the reduction product **3.14e** and no migration product **3.13e** was found. The results show that this type of rearrangement occurs for R^1 = phenyl and phenyl substituted by both electron-withdrawing and electron-donating groups.

[2,3]- And, to a much lesser extent, [1,2]-aza-Wittig rearrangements have been studied mechanistically and for synthetic application by several groups during the last three decades [97S497]. A detailed study of the [1,2]-anionic rearrangement by Eisch and Kovacs in 1971 reported the rearrangement tendencies of the benzylic anions obtained from benzyldiphenylamine and *N*-benzylcarbazole [71JOMC97]. In 1972, Durst et al. reported the base-induced ring enlargements of 1-benzyl- and 1-allyl-2-azetidinones *via* [1,2]- or [2,3]-aza-Wittig rearrangement [72JA9261]. Reetz *et al.* found (9-lithio-9-fluorenyl)allylmethyl amine underwent an aza-Wittig rearrangement when refluxed in THF, but it is not clear whether this is a [1,2]- or [2,3]-shift [75TL3485]. Reductive lithiation of *N*-allyl-*N*-heptyl-*N*-[(phenylsulfanyl)methyl]amine yielded a homoallylic amine, claimed as a [2,3]-sigmatropic rearrangement [89JA2981]. However, Nakai *et al.*

found later that a similar reductive desulfurization did not afford a [2,3]-shifted product, instead it gave a 4:1 mixture of the reduction product and the [1,2]-shifted product [90CL2069]. Gawley *et al.* demonstrated that an [2,3]-aza-Wittig rearrangement proceeds with inversion of configuration at the lithium-bearing carbon, which was itself formed through tin-lithium exchange [95JA11818]. Somfai *el al.* studied the mechanistic, scope and limitation of the [2,3]-aza-Wittig rearrangements of vinylaziridines [96TL2495, 96JOC8148]. Coldham and his co-workers demonstrated that the [1,2]-aza-Wittig occurred in certain *N*-benzylaminomethylstannanes [93JCS(P1)1275], whereas the [2,3]-route was adopted for 2-benzoylaziridines [95JCS(P1)2739, 95TL3557] and *N*-alkyl-*N*-allyl amino esters [98JCS(P1)2817]. This previous work concentrated on the [2,3]-aza-Wittig, with much less comment on the alternative [1,2]-mechanism. To our best knowledge, SmI_2 has not previously been used as a reductive agent to induce the [1,2]-aza-Wittig rearrangement and no report was found of benzyl and/or substituted benzyl as a migrating group.

3.3 Conclusion

In conclusion, we have demonstrated the capacity of the 6-exo-α-aminoalkyl radical cyclizations to form a variety of piperidine derivatives. Syntheses of piperidines are well documented [94TL999, 95MI1, 98JOC566, 98JOC566, 88JOC5491, 97T8447, 98TL6927, 98JOC2711, 98JOC6699] due to their presence in numerous natural products and their biological properties [83JMC1747, 85JMC699, 85JMC1934, 85JMC1943, 85JMC1925]. To the best of our knowledge, no previous procedures have been reported using the cycloaddition of unstable α-aminoalkyl radicals to unactivated double bonds as a means to prepare piperidine derivatives. In compound **3.3e** (R = Ph), [1,2]-aza-Wittig rearrangement occurred instead of cyclization and further [1,2]-aza-Wittig rearrangements were studied using **3.12a-e** as starting materials. This work significantly extends the scope of the previously little studied [1,2]-aza-Wittig rearrangement.

3.4 Experimental Section

General Comments. Melting points were determined on a hot stage apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ with TMS or $CHCl_3$ as internal reference. The spectra of compound **3.8d** were taken on a Varian Inova at 500 MHz for ^{1}H, in CD_3Cl. Elemental analyses were performed on a Carlo Erba-1106 instrument. High resolution mass spectra were measured on a Kratos/AE1-MS 30 mass spectrometer. GC-MS analyses were run on a Hewlett Packard 5890 Series II Gas Chromatograph HP-5 (30 m × 0.32 mm × 0.25 μm) capillary column with a HP 5972 Series Mass Selective Detector. THF and ether were distilled from sodium/benzophenone under nitrogen immediately prior to use. HMPA was dried over molecular sieves. All reactions with air-sensitive compounds were carried out under an argon atmosphere.

General Procedure for the Preparation of Benzotriazole Derivatives **3.3a-e** and **3.12a-e.** *N*-Benzyl-*N*-(4-pentenyl) amine **3.1** (for **3.3a-e**, 2.0 mmol) or *N*-benzyl-*N*-butyl amine (for **3.12a-e**, 2.0 mmol) corresponding aldehyde (2.0 mmol) and benzotriazole (2.1 mmol) were mixed in 25 mL dry ether with 4Å molecular sieves and stirred for 12 h before the resulting solution was filtered through celite and washed using a small amount of dry diethyl ether. The solvent was removed under vacuum to yield **3.3a-d** as an oil. They were used in a crude form for the preparative purpose. For **3.3e** and **3.12a-e**, the solids were obtained after solvent was removed. Recrystallized form dry diethyl ether yielded a white crystalline as the desired product.

N-[Benzotriazol-1-yl(phenyl)methyl]-*N*-benzyl-4-penten-1-amine (**3.3e**).

mp 112–114 °C. Yield: 60%. ^{1}H NMR δ 1.62–1.68 (m, 2H), 1.90–1.97 (m, 1H), 2.03–2.13 (m, 1H), 2.50–2.59 (m, 1H), 2.94–3.07 (m, 1H), 3.41 (d, J = 4.3 Hz, 1H), 4.18 (d, J = 4.3 Hz, 1H), 4.87 (d, J = 1.4 Hz, 1H), 4.94 (d, J = 9.3 Hz, 1H), 5.64–5.75 (m, 1H), 6.90 (s, 1H), 7.04–7.12 (m, 2H), 7.20–7.46 (m, 10H), 8.12–8.15 (m, 1H); ^{13}C NMR δ 27.6, 31.2, 49.4, 54.2, 85.0, 110.7, 114.7, 118.6, 120.0, 123.9, 126.3, 127.1, 127.4, 128.4, 128.5, 128.6, 128.7, 136.9, 138.2, 138.8, 145.6. HRMS (CI) *m/z* calcd for $C_{25}H_{27}N_4$: 383.2236 (M + 1). Found: 383.2252 (M + 1).

N-[Benzotriazol-1-yl(phenyl)methyl]-*N*-benzyl-1-butan amine (**3.12a**).

mp 100–102 °C. Yield: 69%. ^{1}H NMR δ 0.82 (t, J = 7.2 Hz, 3H), 1.18–1.45 (m, 2H), 1.52–1.61 (m, 2H), 2.46–2.60 (m, 1H), 2.95–3.06 (m, 1H), 3.41 (d, J = 14.3 Hz, 1H), 4.19 (d, J = 14.3 Hz, 1H), 6.92 (s, 1H), 7.05–7.42 (m, 12H), 7.82–7.98 (m, 1H), 8.13–8.16 (m, 1H); ^{13}C NMR δ 13.9, 20.2, 30.4, 49.5, 54.1, 77.5, 110.7, 120.0, 123.8, 127.0, 127.3, 127.4, 128.3, 128.4, 128.5, 128.6, 134.0, 136.9, 138.9, 145.6. Anal. Calcd for $C_{24}H_{26}N_4$: C, 77.80; H, 7.07; N, 15.12. Found: C, 77.47; H, 7.22; N, 15.49.

N-[Benzotriazol-1-yl(4-fluorophenyl)methyl]-*N*-benzyl-1-butanamine (**3.12b**).

mp 77–79 °C. Yield: 80%. ^{1}H NMR δ 0.83 (t, J = 7.2 Hz, 3H), 1.22–1.24 (m, 2H), 1.53–1.60 (m, 2H), 2.48–2.52 (m, 1H), 2.95–3.18 (m, 1H), 3.39 (d, J = 14.3 Hz, 1H), 4.17 (d, J = 14.3 Hz, 1H), 6.87 (s, 1H), 6.99–7.47 (m, 11H), 7.81–7.97 (m, 1H), 8.15–8.18 (m, 1H); ^{13}C NMR δ 13.9, 20.2, 30.4, 49.4, 54.0, 77.2, 110.5, 115.4 (d, J =

22.5 Hz), 120.0, 124.0, 127.2, 127.4, 128.2, 128.5 (d, $J = 7.5$ Hz), 129.1, 132.7, 134.0, 138.7, 145.5, 162.6 (d, $J = 247.5$Hz). Anal. Calcd for $C_{24}H_{25}FN_4$: C, 74.20; H, 6.49; N, 14.42. Found: C, 74.30; H, 6.63; N, 14.75

N-[Benzotriazol-1-yl(phenyl)methyl]-*N*-(4-methylbenzyl)-1-butanamine (**3.12c**).

mp 83–85 °C. Yield: 51%. ^{1}H NMR δ 0.84 (t, $J = 7.2$ Hz, 3H), 1.23–1.54 (m, 2H), 1.57–1.68 (m, 2H), 2.37 (s, 3H), 2.46–2.55 (m, 1H), 2.96–3.05 (m, 1H), 3.36 (d, $J = 14.2$, 1H), 4.16 (d, $J = 14.2$ Hz, 1H), 6.91 (s, 1H), 7.06–7.45 (m, 11H), 7.93–8.05 (m, 1H), 8.15–8.17 (m, 1H); ^{13}C NMR δ 13.9, 20.2, 21.1, 30.4, 49.4, 53.7, 77.0, 110.8, 115.1, 119.9, 123.9, 127.3, 128.3, 128.6, 129.0, 129.1, 129.2, 129.7, 134.4, 135.7, 137.0. HRMS (CI) *m/z* calcd for $C_{25}H_{29}N_4$: 385.2392 (M + 1). Found: 385.2408 (M + 1).

N-[Benzotriazol-1-yl(phenyl)methyl]-*N*-(4-fluorobenzyl)-1-butanamine (**3.12d**).

mp 84–86 °C. Yield: 44%. ^{1}H NMR δ 0.81 (t, $J = 7.3$ Hz, 3H), 1.10–1.40 (m 2H), 1.42–1.61 (m, 2H), 2.38–2.50 (m, 1H), 2.83–3.00 (m, 1H), 3.42 (d, $J = 14.3$ Hz, 1H), 4.13 (d, $J = 14.3$ Hz, 1H), 6.89 (s, 1H), 6.99–7.45 (m, 10H), 7.91–7.97 (m, 1H), 8.08–8.18 (m, 1H); ^{13}C NMR δ 13.9, 20.2, 30.4, 49.5, 53.3, 77.0, 110.6, 115.3 (d, $J = 22.5$ Hz), 118.5, 120.0, 123.9, 126.3, 127.1, 127.3, 128.4, 128.6, 130.1 (d, $J = 7.5$Hz), 136.8, 145.6, 165.5 (d, $J = 225.0$Hz). Anal. Calcd for $C_{24}H_{25}FN_4$: C, 74.20; H, 6.49; N, 14.42. Found: C, 73.88; H, 6.54; N, 14.76.

N-[Benzotriazol-1-yl(phenyl)methyl]-*N*-butyl-2-furyl amine (**3.12e**).

mp 77–79 °C. Yield: 65%. ^{1}H NMR δ 0.81 (t, $J = 7.1$ Hz, 3H), 1.20–1.37 (m, 2H), 1.47–1.56 (m, 2H), 2.50–2.56 (m, 1H), 2.83–2.90 (m, 1H), 3.51 (d, $J = 14.8$ Hz, 1H), 4.13 (d, $J = 14.8$ Hz, 1H), 6.18 (d, $J = 3.0$ Hz, 1H), 6.30 (d, $J = 3.0$ Hz, 1H), 7.00 (s, 1H), 7.23–7.39 (m, 8H), 7.85–9.00 (m, 1H), 8.12–8.14 (m, 1H); ^{13}C NMR δ 13.8, 20.0, 30.0, 47.0, 49.3, 78.3, 108.6, 110.1, 110.8, 119.9, 123.8, 127.1, 127.5, 128.4, 128.6, 133.7, 136.6, 142.2, 145.7, 152.3. Anal. Calcd for $C_{22}H_{24}N_4O$: N, 15.54. Found: N, 15.84.

General Procedure for the Preparation of Piperidine Derivatives **3.7a-c** and **3.8a-f.** Compound **3.3a-c** (2 mmol) in THF (20 mL) was added dropwise to the solution of SmI_2 in THF (60 mL, 0.1 M) and HMPA (6 mL) at 0 °C. After the addition was finished, the mixture was stirred for further 10 min and electrophile (2.5 mmol) was added. The reaction mixture was allowed to rise to room temperature overnight. The reaction mixture was extracted with ether (3 × 40 mL). The combined organic layer was dried over Na_2SO_4. After evaporation under vacuum, the residue was purified by flash chromatography (silica gel saturated with Et_3N) using hexanes : EtOAc = 100 : 0.5 as eluent to afford desired product **3.7a-c** or **3.8a-f**. (For compounds **3.7a-c**, no electrophile was used)

1-Benzyl-3-methyl-2-propyl piperidine (**3.7a**).

Oil. Yield: 56%. (single isomer) ^{1}H NMR δ 0.87 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H), 1.21–1.76 (m, 8H), 1.85–2.18 (m, 1H), 2.21–2.36 (m, 1H), 2.37–2.60 (m, 2H), 3.68, 3.75 (AB, *J* = 13.8 Hz, 2H), 7.13–7.47 (m, 5H); ^{13}C NMR δ 14.5, 17.5, 21.8, 22.9, 27.0, 29.1, 31.8, 47.1, 58.3, 63.1, 126.5, 128.0, 128.6, 140.9. HRMS (CI) *m/z* calcd for $C_{16}H_{26}N$: 232.2065 (M + 1). Found): 232.2042 (M + 1).

1-Benzyl-2-isopropyl-3-methyl piperidine (**3.7b**).

Oil. Yield: 51%. (single isomer) ^{1}H NMR δ 0.96 (d, *J* = 6.7 Hz, 3H), 1.00–1.12 (m, 6H), 1.12–1.30 (m, 1H), 1.52–1.80 (m, 3H), 1.92–2.15 (m, 2H), 2.20–2.35 (m, 2H), 2.81 (dd, *J* = 13.0, 3.6 Hz, 1H), 3.53, 3.94 (AB, *J* = 14.0, 2H), 7.16–7.42 (m, 5H); ^{13}C

NMR δ 16.1, 17.4, 20.0, 20.7, 27.7, 29.5, 33.1, 51.2, 54.1, 69.1, 126.3, 128.1, 141.6. HRMS (CI) *m/z* calcd for $C_{16}H_{26}N$: 232.2065 (M + 1). Found: 232.2099 (M + 1).

3-[(1-Benzyl-2-propyl-3-piperidinyl)methyl]-3-pentanol (**3.8a**).

Oil. Yield: 51%. (single isomer) ^{1}H NMR δ 0.68–0.93 (m, 9H), 1.10–1.30 (m, 5H), 1.30–1.40 (m, 2H), 1.40–1.55 (m, 4H), 1.55–1.75 (m, 4H), 1.97–2.12 (m, 1H), 2.35–2.49 (m, 1H), 2.50–2.70 (m, 2H), 3.70, 3.80 (AB, *J* = 13.5 Hz, 2H), 7.13–7.39 (m, 5H); ^{13}C NMR δ 7.9, 8.0, 14.5, 22.1, 22.9, 26.5, 28.2, 31.2, 31.4, 32.0, 41.1, 44.9, 58.4, 63.0, 75.5, 126.5, 128.0, 128.6, 140.7. Anal. Calcd for $C_{21}H_{35}NO$: C, 79.44; H, 11.11; N, 4.41. Found: C, 79.02; H, 11.55; N, 4.87.

1-(Benzyl-2-propyl-3-piperidinyl)-2-methyl-2-butanol (**3.8b**).

Oil. Yield: 43%. (mixture of two isomers) ^{1}H NMR δ 0.89 (t, *J* = 7.4 Hz, 6H), 1.16 (s, 3H), 1.02–1.42 (m, 7H), 1.43–1.73 (m, 6H), 1.97–2.11 (m, 1H), 2.35–2.48 (m, 1H), 2.50–2.68 (m, 2H), 3.70, 3.80 (AB, *J* = 13.6 Hz, 2H), 7.15–7.45 (m, 5H); ^{13}C NMR δ 8.3, 8.4, 14.5, 22.1, 22.2, 22.8, 22.9, 26.6, 26.7, 26.8, 28.2, 28.3, 29.7, 32.6, 32.8, 34.8, 35.2, 43.8, 43.9, 44.0, 44.8, 45.0, 58.4, 63.0, 63.1, 73.6, 126.5, 128.0, 128.5, 140.7. Anal. Calcd for $C_{20}H_{33}NO$: C, 79.15; H, 10.96; N, 4.62. Found: C, 79.30; H, 11.19; N, 4.81.

1-(Benzyl-2-propyl-3-piperidinyl)-2-methyl-2-pentanol (**3.8c**).

Oil. Yield: 41%. (mixture of two isomers) ^{1}H NMR δ 0.77–0.98 (m, 6H), 1.05 –1.20 (m, 4H), 1.20–1.52 (m, 12H), 1.56–1.74 (m, 2H), 1.96–2.12 (m, 1H), 2.36–2.48 (m, 1H), 2.49–2.70 (m, 2H), 3.70, 3.80 (AB, *J* = 13.4 Hz, 2H), 7.16–7.40 (m, 5H); ^{13}C NMR δ 14.5, 14.6, 17.2, 17.3, 22.1, 22.2, 22.8, 22.9, 26.5, 26.6, 27.1, 27.4, 28.2, 28.3, 29.7, 32.5, 32.8, 44.5, 44.9, 45.1, 45.2, 58.4, 62.9, 63.0, 73.5, 126.6, 128.0, 128.6, 140.6.

Anal. Calcd for $C_{21}H_{35}NO$: C, 79.44; H, 11.11; N, 4.41. Found: C, 79.45; H, 11.38; N, 4.54.

2-(1-Benzyl-2-propyl-3-piperidinyl)-1-phenyl-1-ethanol (**3.8d**).

Oil. Yield: 17%. (single isomer) ^{1}H NMR δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.25–1.43 (m, 4H), 1.50–1.65 (m, 4H), 1.72–1.83 (m, 2H), 2.04–2.12 (m, 1H), 2.15–2.25 (m, 1H), 2.46–2.59 (m, 1H), 2.67–2.80 (m, 1H), 3.42, 3.92 (AB, *J* = 11.2 Hz, 2H), 4.78 (dd, *J* = 9.0, 4.4 Hz, 1H), 7.20–7.40 (m, 10H); ^{13}C NMR δ 14.5, 21.0, 22.4, 22.9, 27.6, 29.7, 33.5, 41.7, 58.0, 62.4, 71.7, 125.9, 126.9, 127.3, 128.2, 128.4, 129.0, 139.2, 145.6. HRMS (CI) *m/z* calcd for $C_{23}H_{32}NO$: 338.2484 (M + 1). Found: 338.2480 (M + 1).

1-(1-Benzyl-2-propyl-3-piperidinyl)-2-propanol (**3.8e**).

Oil. Yield: 21%. (single isomer) ^{1}H NMR δ 0.93 (t, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 6.1 Hz, 3H), 1.10–1.30 (m, 5H), 1.20–1.50 (m, 2H), 1.50–1.90 (m, 5H), 2.30–2.47 (m, 2H), 2.48–2.60 (m, 1H), 3.50–3.65 (m, 2H), 3.86–4.00 (m, 1H), 7.16–7.45 (m, 5H); ^{13}C NMR δ 14.4, 20.8, 22.7, 24.1, 26.1, 29.7, 33.5, 45.2, 45.7, 59.1, 63.0, 65.2, 126.9, 128.2, 129.1, 138.9. HRMS (CI) *m/z* calcd for $C_{18}H_{30}NO$: 276.2327 (M + 1). Found: 276.2330 (M + 1).

2-(1-Benzyl-2-propyl-3-piperidinyl)-N-isopropylacetamide (**3.8f**).

Oil. Yield: 25%. (single isomer) ^{1}H NMR δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.13 (d, *J* = 6.6 Hz, 6H), 1.18–1.30 (m, 1H), 1.30–1.48 (m, 4H), 1.50–1.88 (m, 5H), 1.90–2.68 (m, 4H), 3.62, 3.78 (AB, *J* = 13.7 Hz, 2H), 3.92–4.17 (m, 1H), 5.18–5.33 (m, 1H), 7.15–7.45 (m, 5H); ^{13}C NMR δ 14.5, 21.1, 21.2, 22.8, 22.9, 26.6, 27.8, 29.7, 34.2, 39.5, 41.2, 58.1, 61.8, 126.6, 128.1, 128.6, 140.6, 171.5. HRMS (CI) *m/z* calcd for $C_{20}H_{33}N_2O$: 317.2593 (M + 1). Found: 317.2594 (M + 1).

General Procedure for [1,2]-Aza-Wittig Rearrangement. The solution of compound **3.3e** or **3.12a-e** (2mmol) in THF (20 mL) was added dropwise to the mixed solution of 0.1 M SmI_2 in THF (60 mL) and HMPA (6 mL) at 0 °C within 20 min. After an additional 20 min, the reaction mixture was warmed to room temperature and stirred overnight. A saturated K_2CO_3 aqueous solution was added to quench the reaction. Ethyl acetate (150 mL) was added and the aqueous solution was removed. The organic solution was dried over anhydrous Na_2SO_4 and solvent was removed *in vacuo*. The residue was subjected to silicon gel chromatography to yield the rearrangement and reductive product, respectively.

N-(1,2-Diphenylethyl)-4-penten-1-amine (**3.10**).

Oil. Yield: 20%. ^{1}H NMR δ 1.43–1.50 (m, 2H), 1.89–1.95 (m, 2H), 2.36–2.42 (m, 2H), 2.91 (d, J = 6.9 Hz, 2H), 3.83 (t, J = 6.9 Hz, 1H), 4.85 (d, J = 10.7 Hz, 1H), 4.88 (d, J = 1.5 Hz, 1H), 5.60–5.76 (m, 1H), 7.09–7.35 (m, 10H); ^{13}C NMR δ 29.1, 31.3, 45.3, 47.0, 64.7, 114.5, 126.3, 127.0, 127.3, 128.3, 128.4, 129.3, 138.4, 139.0, 144.0. HRMS (CI) *m/z* calcd for $C_{19}H_{24}N$: 266.1909 (M + 1). Found: 266.1909 (M + 1).

N,N-Dibenzyl-4-penten-1-amine (**3.11**).

Oil. Yield: 18%. ^{1}H NMR δ 1.55–1.64 (m, 2H), 2.01–2.07 (m, 2H), 2.44 (t, J = 7.4 Hz, 2H), 3.56 (s, 4H), 4.89 (d, J = 10.6 Hz, 1H), 4.97 (d, J = 1.4 Hz, 1H), 5.68–5.82 (m, 1H), 7.21–7.39 (m, 10H); ^{13}C NMR δ 26.5, 31.5, 53.0, 58.4, 114.3, 126.7, 128.1, 128.8, 138.8, 140.0. Anal. Calcd for $C_{19}H_{23}N$: N, 5.28. Found: N, 5.55.

N-(1,2-Diphenylethyl)-1-butan amine (**3.13a**).

Oil. Yield: 40%. ^{1}H NMR δ 0.82 (t, J = 7.2 Hz, 3H), 1.15–1.30 (m, 2H), 1.30–1.42 (m, 2H), 2.30–2.50 (m, 2H), 2.95 (d, J = 6.9 Hz, 2H), 3.87 (t, J = 6.9 Hz, 1H), 7.13 (d, J = 7.4 Hz, 2H), 7.21–7.49 (m, 8H); ^{13}C NMR δ 13.9, 20.3, 32.1, 45.2, 47.5, 64.9, 126.3, 127.0, 127.3, 128.3, 128.4, 129.3, 138.9, 143.9. HRMS (CI) *m/z* calcd for $C_{18}H_{24}N$: 254.1909 (M + 1). Found: 254.1925 (M + 1).

N-[1-(4-Fluorophenyl)-2-phenylethyl]-1-butan amine (**3.13b**).

Oil. Yield: 60%. ^{1}H NMR δ 0.81 (t, J = 7.2 Hz, 3H), 1.18–1.26 (m, 2H), 1.31–1.39 (m, 2H), 2.33–2.38 (m, 2H), 2.87 (d, J = 7.2 Hz, 2H), 3.82 (t, J = 7.2 Hz, 1H), 7.00 (t, J = 8.2 Hz, 2H), 7.14 (d, J = 9.0 Hz, 2H), 7.22–7.33 (m, 5H); ^{13}C NMR δ 13.9, 20.3, 32.1, 45.4, 47.4, 64.2, 115.0 (d, J = 22.5 Hz), 126.3, 128.4, 128.6 (d, J = 7.5Hz), 129.2, 138.7, 139.6, 161.8 (d, J = 240.0 Hz). Anal. Calcd for $C_{18}H_{22}FN$: C, 79.67; H, 8.17; N, 5.16. Found: C, 79.42; H, 8.36; N, 5.21.

N-[2-(4-Methylphenyl)-1-phenylethyl]-1-butan amine (**3.13c**).

Oil. Yield: 60%. ^{1}H NMR δ 0.83 (t, J = 7.2 Hz, 3H), 1.17–1.25 (m, 2H), 1.29–1.40 (m, 2H), 2.34 (s, 3H), 2.35–2.43 (m, 2H), 2.80–2.95 (m, 2H), 3.83 (t, J = 7.4 Hz, 1H), 6.98–7.12 (m, 4H), 7.26–7.34 (m, 5H); ^{13}C NMR δ 13.9, 20.3, 21.0, 32.2, 44.9, 47.5, 64.9, 126.9, 127.3, 128.2, 129.0, 129.1, 135.8, 142.9, 144.2. HRMS (CI) *m/z* calcd for $C_{19}H_{26}N$: 268.2065 (M + 1). Found: 268.2065 (M + 1).

N-[2-(4-Fluorophenyl)-1-phenylethyl]-1-butan amine (**3.13d**).

Oil. Yield: 57%. ^{1}H NMR δ 0.83 (t, J = 7.2 Hz, 3H), 1.18–1.31 (m, 2H), 1.32–1.54 (m, 2H), 2.30– 2.50 (m, 2H), 2.88 (d, J = 7.1 Hz, 2H), 3.78 (t, J = 7.1 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.99–7.06 (m 2H), 7.23–7.32 (m, 5H); ^{13}C NMR δ 13.9, 20.3, 32.2, 44.4, 47.5, 65.0, 115.1 (d, J = 22.5Hz), 127.0, 127.2, 128.3, 130.6 (d, J = 7.5Hz), 134.5, 143.7, 160.1 (d, J = 247.5 Hz). HRMS (CI) *m/z* calcd for $C_{18}H_{23}N$: 272.1815 (M + 1). Found: 272.1818 (M + 1).

N,N-Dibenzyl-1-butan amine (**3.14a**).

Oil. Yield: 27%. ^{1}H NMR δ 0.83 (t, *J* = 7.2 Hz, 3H), 1.25–1.30 (m, 2H), 1.35–1.42 (m, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 3.55 (s, 4H), 7.21–7.38 (m, 10H); ^{13}C NMR δ 14.0, 20.4, 29.2, 53.1, 58.2, 126.7, 128.1, 128.7, 140.0. HRMS (CI) *m/z* calcd for $C_{18}H_{24}N$: 254.1909 (M + 1). Found: 254.1862 (M + 1).

N-Benzyl-*N*-(4-fluorobenzyl)-1-butan amine (**3.14b**).

Oil. Yield: 23%. ^{1}H NMR δ 0.84 (t, *J* = 7.1 Hz, 3H), 1.20–1.38 (m, 2H), 1.45–1.58 (m, 2H), 2.40 (t, *J* = 7.1 Hz, 2H), 3.51 (s, 2H), 3.54 (s, 2H), 6.99 (t, *J* = 8.6 Hz, 2H), 7.24–7.40 (m, 7H); ^{13}C NMR δ 14.0, 20.4, 29.1, 53.0, 57.5, 58.2, 114.9 (d, *J* = 22.5 Hz), 126.8, 128.2, 128.8, 130.1(d, *J* = 7.5 Hz), 131.5, 140.0, 161.8 (d, *J* = 232.5Hz). Anal. Calcd for $C_{18}H_{22}FN$: C, 79.67; H, 8.17; N, 5.16. Found: C, 79.78; H, 8.41; N, 5.22.

N-Benzyl-*N*-(4-methylbenzyl)-1-butan amine (**3.14c**).

Oil. Yield: 29%. ^{1}H NMR δ 0.86 (t, *J* = 7.1 Hz, 3H), 1.20–1.35 (m, 2H), 1.42–1.55 (m, 2H), 2.35 (s, 3H), 2.42 (t, *J* = 7.4 Hz, 2H), 3.54 (s, 2H), 3.56 (s, 2H), 7.28 (d, *J* = 6.6 Hz, 2H), 7.32–7.46 (m, 7H); ^{13}C NMR δ 14.0, 20.4, 21.1, 29.7, 52.8, 57.7, 57.9, 126.9, 128.2, 128.6, 128.9, 129.0, 129.7, 129.8, 136.5. HRMS (CI) *m/z* calcd for $C_{19}H_{26}N$: 268.2065 (M + 1). Found: 268.2066 (M + 1).

N-Benzyl-*N*-(2-furylmethyl)-1-butan amine (**3.14e**).

Oil. Yield: 100%. ^{1}H NMR δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.29–1.36 (m, 2H), 1.48–1.57 (m, 2H), 2.46 (t, *J* = 7.2 Hz, 2H), 3.61 (s, 2H), 3.64 (s, 2H), 6.19 (d, *J* = 3.0 Hz, 1H), 6.34 (d, *J* = 3.0 Hz, 1H), 7.23–7.42 (m, 6H); ^{13}C NMR δ 13.9, 20.4, 29.2, 49.3, 52.9, 57.9, 108.3, 109.9, 126.7, 128.1, 128.8, 139.4, 141.7, 152.7. Anal. Calcd for $C_{16}H_{21}NO$: N, 5.76. Found: N, 6.01.

CHAPTER 4

N-BOC-*N*-(BENZOTRIAZOL-1-YLMETHYL)BENZYLAMINE AS A 1,1-DIPOLE EQUIVALENT IN STEREOSELECTIVE SYNTHESIS OF 4,5-DISUBSTITUTED IMIDAZOLIDIN-2-ONES

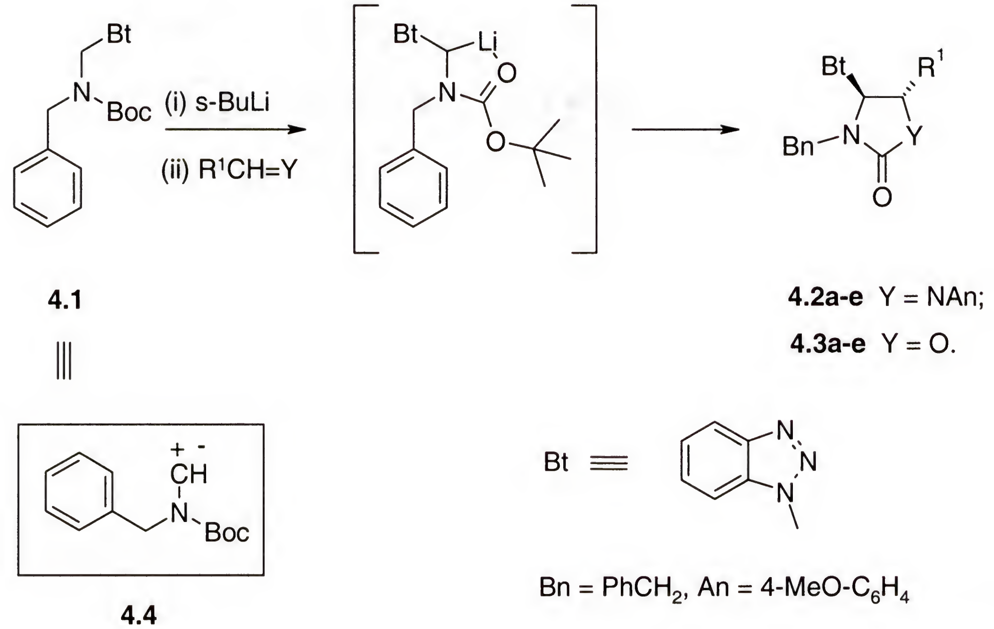
4.1 Introduction

The formation and reactions of dipole-stabilized carbanions adjacent to nitrogen atoms have been well documented [84CR471, 99JOC2996, 96JA715, 96JOC428, 96JA3757, 93JOC1109, 91JOC1564]. Benzyl or allyl activation can supplement dipole stabilization in the formation of the carbanion intermediate [84CR471], but heteroaromatic ring activation to generate a carbanion between two nitrogen atoms, to the best of our knowledge, has not been well studied. Since benzotriazole activates an α-CH toward proton loss more than phenyl or vinyl [98CR409], *N*-Boc-*N*-(benzotriazol-1-ylmethyl)benzylamine (**4.1**) should be lithiated selectively at the carbon adjacent to the benzotriazole residue. Benzotriazole α to a hetereoatom can act as a good leaving group to form a carbocation. We now report that *N*-Boc-*N*-(benzotriazol-1-ylmethyl) benzylamine (**4.1**) can behave as the 1,1-dipole equivalent **4.4** (cf Scheme 4.1) for the stereoselective synthesis of 4,5-disubstituted-4,5-dihydroimidazolidin-2-ones **4.5a-k** (Scheme 4.2) *via* benzotriazole intermediates of type **4.2**.

4,5-Disubstituted 4,5-dihydroimidazolidin-2-ones are protected precursors of vicinal diamines. Vicinal diamine structural units are very important in biologically active natural products, in medicinal chemistry, and in the asymmetric synthesis as chiral ligands and chiral auxiliaries [98AG(E)2581, 98AC2446, 99JOC1958]. Thus, it is still of considerable interest to explore novel synthetic routes for this type of compounds although a number of methods have been reported. Previous methods for the stereoselective generation of 1,2-diamines comprise: (i) transformations of diols, diazides [90S1023], aziridines [94TL7395, 91TL4045], and α-bromo oxime ethers [92LAC1005]; (ii) reduction of diimines derived from diketones or dialdehydes [92JOC6653, 96AG(E)2261]; (iii) reduction of 2-aminonitroalkanes [93TL4743]; (iv) conversion of enantiopure amino acids [91AG(E)103]; (v) the addition of Grignard reagents to α-amino nitrones [97T(A) 2381]; (vi) the addition of α-nitrogen carbanions to imine [96JOC428, 96JA3757]s; (vii) aza-Michael additions to nitroalkenes [96S1443]; (viii) nitro-Mannich reactions [98JOC9932]; and (ix) the use of chiral auxiliaries [97JOC4180]. Although reaction of stabilized α-nitrogen carbanions with imines affords *trans*-4,5-dihydroimidazolidin-2-ones in good yields and with good stereoselectivities, the examples published [96JOC428, 96JA3757] are limited to the preparation of 4-aryl and 4,5-diaryl derivatives. The present method using *N*-Boc-*N*-(benzotriazol-1-ylmethyl) benzylamine as a 1,1-dipole synthon enables the efficient introduction of a variety of substituents at the 4 position of 5-aryl- and 5-heteroaryl-4,5-dihydroimidazolidin-2-ones stereospecifically and in good yields.

4.2 Results and Discussion

Preparation of Benzotriazolyl-imidazolidinone Derivatives **4.2a-e**. Starting material **4.1** is easily synthesized by a two-step procedure. Protection of benzylamine with $(Boc)_2O$ afforded *N*-Boc-benzylamine [96JA715], which reacted further (without purification) with formaldehyde and benzotriazole in the presence of a catalytic amount



4.1

4.4

4.2a-e Y = NAn;

4.3a-e Y = O.

Bn = $PhCH_2$, An = 4-MeO-C_6H_4

Scheme 4.1

Table 4.1. Preparation of Benzotriazole Derivatives **4.2a-e** and **4.3a-e**.

Entry	R^1	Product	Yield (%)	Product	Yield (%)
1	Ph	**4.2a**	82	**4.3a**	82
2	4-Me-C_6H_4	**4.2b**	74	**4.3b**	76
3	4-MeO-C_6H_4	**4.2c**	80	**4.3c**	72
4	4-F-C_6H_4	**4.2d**	61	**4.3d**	70
5	2-Furyl	**4.2e**	70	**4.3e**	66

of TsOH using a Dean-Stark apparatus to remove the water azeotropically, to give *N*-Boc-*N*-(benzotriazol-1-ylmethyl)benzylamine (**4.1**) in 70% overall yield. Treatment of **4.1** with 1 equiv of *s*-BuLi in THF at –78 °C for 0.5 h, followed by the addition of imines as electrophiles produced the benzotriazolyl-substituted imidazolidinones **4.2a-e** (Scheme

4.1). When imines derived from aromatic aldehydes (electron-donating substituent, entry 3; electron-withdrawing substituent, entry 4) or a hetereoaromatic aldehyde (entry 5) were used, benzotriazole derivatives **4.2** were obtained in good yields (Table 4.1) and stereospecifically (*trans*:*cis* > 99:1). According to the ^{1}H NMR and ^{13}C NMR spectra, only one isomer was observed and isolated from the reaction mixture in each case.

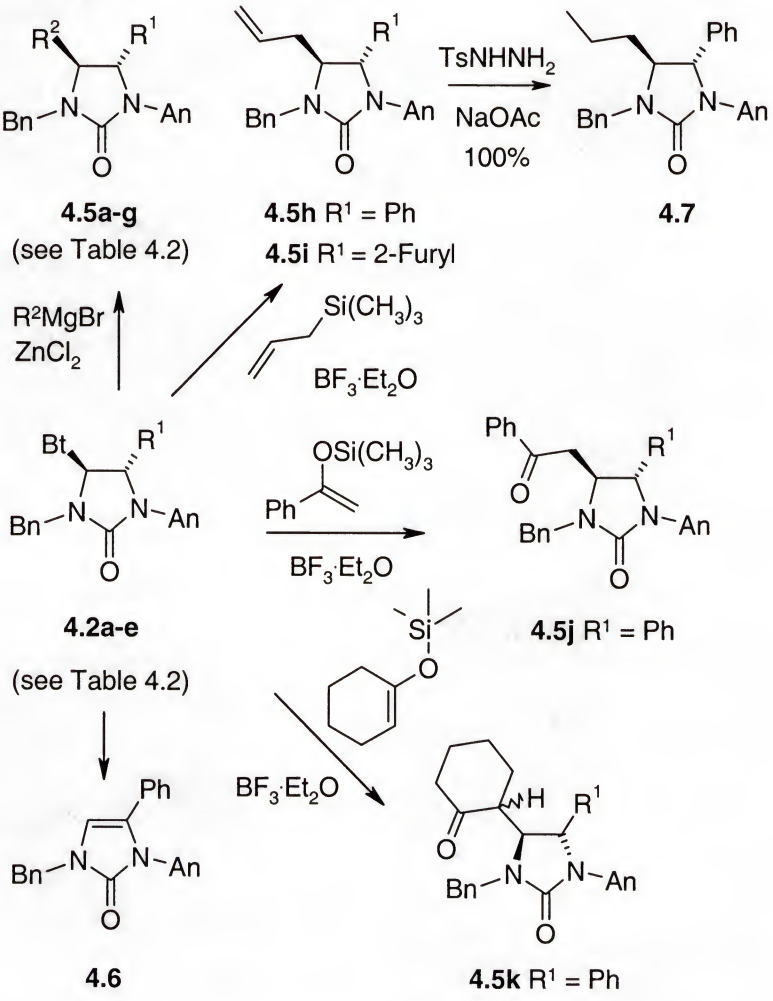
Reaction of Synthon **4.2** with Diverse Organozinc Reagents. Treatment of **4.2a-e** with organozinc reagents gave compounds **4.5a-g** (Scheme 4.2) in good yields and stereospecifically (*trans*:*cis* > 99:1 according to NMR of the reaction mixtures) (Table 4.2). Arylzinc reagents (entries 1-5)**,** an alkynylzinc reagent (entry 6), and an alkenylzinc reagent (entry 7) all afforded the corresponding desired products. Various 5-substituted imidazolidinones **4.2a-e** can be used for these substitution reactions (entries 1-5). However, alkyl zinc reagents produced no desired products but β-H elimination occurred to give compounds like **4.6** together with other products (detailed results will be discussed in Chapter 6).

Reaction of Synthon **4.2** with Allyltrimethylsilane and Vinyloxysilanes. Treatment of **4.2a** with $SnCl_4$ at –78 °C for 30 min followed by the addition of allyltrimethylsilane afforded *trans*-4,5-disubstituted imidazolidinone (**4.5h**) (20%) along with the β-H elimination product **4.6** (50%) (Scheme 4.2). When $BF_3{\cdot}Et_2O$ was used, exclusively **4.5h** was produced in 67% yield (Table 4.2) and with high *trans* selectivity (*trans*:*cis* > 99:1 according to NMR of the reaction mixture). Under the same reaction conditions, **4.5i** was prepared in 40% yield.

Reaction of trimethyl[(1-phenylvinyl)oxy]silane or (1-cyclohexen-1-yloxy) trimethylsilane with **4.2a** gave products **4.5j-k** in good yields and specifically (*trans*:*cis* >

99:1 according to NMR of the reaction mixtures). In the case of **4.5k**, no stereochemical control at the carbon α to carbonyl group in the cyclohexanone substituent was observed. The H4 was shown as a doublet in ^{1}H NMR and the coupling constant between H4 and H5 was 4.0 Hz in **4.5k**, indicating that H4 and H5 was in *trans* configuration.

Compound **4.7** was easily obtained from the reduction of **4.5h** [87JOC4665], which made it possible for the indirect stereospecific introduction of an alkyl group in the 4 position in 4,5-disubstituted-imidazolidinones (Scheme 4.2).

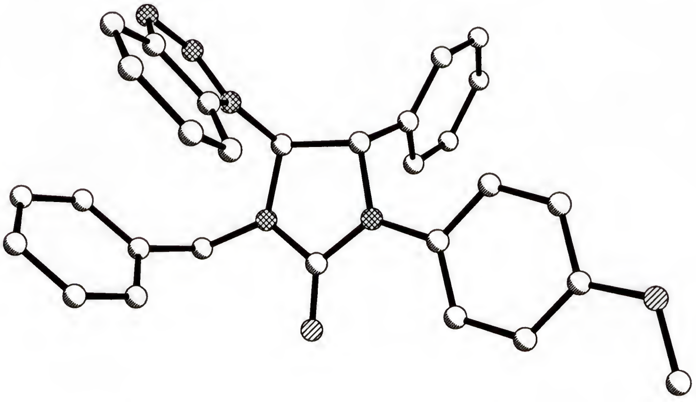


Scheme 4.2

Table 4.2. Substitution of the Benzotriazole Moiety in **4.2a-e** by Carbon Nucleophiles.

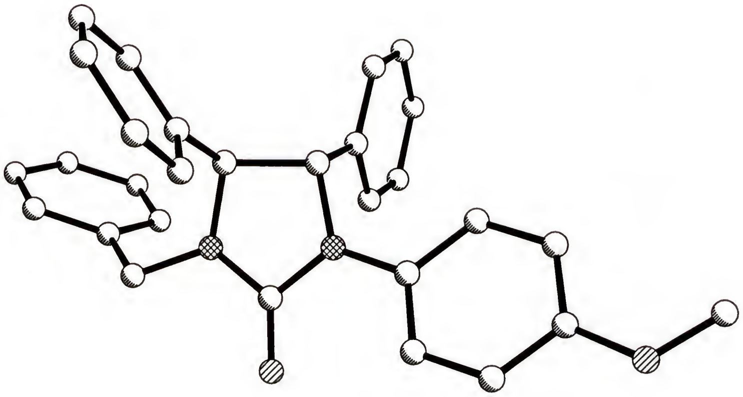
Entry	S.M.	R^1	R^2	Product	Yield (%)
1	**4.2a**	Ph	Ph	**4.5a**	68
2	**4.2b**	4-Me-C_6H_4	Ph	**4.5b**	50
3	**4.2c**	4-MeO-C_6H_4	Ph	**4.5c**	65
4	**4.2d**	4-F-C_6H_4	Ph	**4.5d**	60
5	**4.2e**	2-Furyl	Ph	**4.5e**	66
6	**4.2a**	Ph	Ph-C≡C	**4.5f**	74
7	**4.2a**	Ph	CH_2=CH	**4.5g**	68
8	**4.2a**	Ph	CH_2=CH-CH_2	**4.5h**	67
9	**4.2e**	2-Furyl	CH_2=CH-CH_2	**4.5i**	40
10	**4.2a**	Ph	PhC(=O)CH_2	**4.5j**	64
11	**4.2a**	Ph	*c*-C_4H_8COCH	**4.5k**	70

The *trans* configuration for compounds **4.2a-e**, **4.5a-k**, and **4.7** was assigned from the coupling constant $J_{4,5}$ between H4 and H5 in heterocyclic five-membered rings based on literature reports [93T7787, 97JOC4449] and X-ray crystallography. It is generally accepted that the *trans* coupling constant is smaller than that of the corresponding *cis* coupling in a five-membered heterocyclic ring system. When a vicinal coupling constant is smaller than 4 Hz in a five-membered heterocyclic ring system, the geometry is assigned as *trans* [93T7787]. The coupling constant in 4,5-disubstituted imidazolidin-2-ones **4.2a**-**e** was around 2.5 Hz, so they were assigned *trans* configuration. The full structure and stereochemistry of **4.2a** was further confirmed by a single crystal X-ray structure determination (Figure 4.1). The coupling constant $J_{4,5}$ (around 6.0 Hz) between H4 and H5 in **4.5a** is more ambiguous in terms of stereochemical assignment, but is consistent with similar compounds which have *trans* configurations [96JOC428, 96JA3757]. The structure of **4.5a** was unambiguously determined by X-ray crystallography (Figure 4.2), which confirmed the *trans* stereochemistry. Similarly, the other compounds were also assigned as having *trans* geometry.



Perspective view of the X-ray crystal structure of **4.2a**.
Hydrogen atoms are omitted for clarity.

Figure 4.1



Perspective view of the X-ray crystal structure of **4.4a**.
Hydrogen atoms are omitted for clarity.

Figure 4.2

The high *trans* selectivity for **4.2a**-**e** probably derives from the formation of the products under thermodynamic control; however, products **4.5a**-**k** are all formed under kinetic control indicating that both thermodynamic and kinetic control highly favor *trans* products. In the presence of a Lewis acid (such as *in situ* generated $MgBr_2$ or $BF_3{\cdot}Et_2O$), the benzotriazole moiety in **4.2a**-**e** can be removed to form acyliminium salts, which are attacked by nucleophiles exclusively from the opposite face of the R^1 group affording *trans* products. With basic nucleophiles (such as alkyl in contrast to aryl zinc reagents) or a strong Lewis acid (such as $SnCl_4$ relative to $BF_3{\cdot}Et_2O$ [91COS(1)295]), β-H elimination occurs to give products like **4.6**.

Under similar reaction conditions as for imines, aldehydes were used as electrophiles of lithiated **4.1** to give analogous oxazolidinones **4.3a**-**e** (Scheme 4.1). All the reactions produced the *trans* isomers selectively in good yields when arylaldehydes were used (Table 4.1). The *trans* conformation is based on the coupling constant ($J_{4,5}$ = 2.5 Hz), which is also consistent with the literature report [97JOC4449].

Attempts to substitute the benzotriazole residue in oxazolidinones **4.3a**-**e** failed. When organozinc reagents, organocerium reagents, organocopper reagents, Grignard reagents and allyltrimethyl silanes were used as nucleophiles, either no reactions occurred or only elimination products were isolated. Probably in these 4,5-disubstituted oxazolidin-2-ones **4.3a**-**e**, the single nitrogen atom can not assist the removal of benzotriazole due to its relatively electron deficient character compared to that of the analogous nitrogen atom in 4,5-disubstituted imidazolidin-2-ones **4.2**.

4.3 Conclusion

A general method using *N*-Boc-*N*-(benzotriazol-1-ylmethyl)benzylamine as a 1,1-dipole equivalent to synthesize various *trans*-4,5-disubstituted imidazolidinones was reported. A number of *trans*-4,5-disubstituted imidazolinones were obtained in good yields and with excellent stereoselectivity. Imidazolidin-2-ones can be converted directly into the corresponding secondary diamines under basic conditions (NaOH) without affecting the two *N*-protecting groups [91IJCS(B)399, 96JOPP333]. Alternatively, removal of one or both the *N*-protecting groups [96JOC428, 87T4887], followed by hydrolysis under acidic conditions (HCl or HBr) gives the corresponding primary diamines [91T2263, 90JOC5017, 95TL8607]. Although benzotriazole derivatives **4.3a-e** of 4,5-disubstituted oxazolidin-2-ones could be obtained, attempted displacement of the benzotriazole moiety was not successful.

4.3 Experimental Section

General Comments. Melting points were determined on a hot stage apparatus and are uncorrected. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ with TMS as the internal reference. THF was distilled from sodium/benzophenone and CH_2Cl_2 was distilled from CaH_2 under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under argon atmosphere.

Synthesis of *N*-Boc-*N*-(benzotriazol-1-ylmethyl)benzylamine (**4.1**). Benzylamine (8.56 g, 0.08 mol) and triethylamine (11.7 mL) were mixed in methylene chloride (300 mL) at 0 °C and then di-*tert*-butyl dicarbonate (17.44 g, 0.08 mol) in methylene chloride (100 mL) was added. The solution was stirred overnight, and methylene chloride was removed under reduced pressure. The crude product obtained can be used in the next step without purification.

The crude product, prepared as shown above, benzotriazole (9.52 g, 0.08 mol), paraformaldehyde (2.4 g, 0.08 mol) and a catalytic amount of *p*-toluenesulfonic acid were mixed in toluene (400 mL) and refluxed overnight with a Dean-Stark trap to remove the water formed. After toluene was removed under reduced pressure, the crude product was subjected directly to silica gel column chromatography, and product **4.1** was obtained as white prisms (from methylene chloride and hexanes): mp 126–127 °C. Yield: 70%. ^{1}H NMR δ 1.50 (s, 9H), 4.43 (s, 2H), 6.10 (s, 2H), 7.26–7.41 (m, 7H), 7.51 (t, J = 7.6 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 28.2, 48.7, 57.3, 81.6, 111.0, 119.6, 124.2, 127.6, 127.8, 128.6, 132.5, 136.7, 146.2, 155.2. Anal. Calcd for $C_{19}H_{22}N_4O_2$: C, 67.44; H, 6.55; N, 16.56. Found: C, 67.26; H, 6.70; N, 16.60.

General Procedure for the Synthesis of Compounds **4.2a-e** and **4.3a-e**. At –78 °C, *s*-BuLi (2 mmol, 1.3 M in hexane) was added slowly to a solution of *N*-Boc-*N*-(benzotriazol-1-ylmethyl)benzylamine (**4.1**) (2 mmol) in THF (25 mL), and the reaction mixture was stirred for 0.5 h at this temperature. Then an imine or an aldehyde (2 mmol) in THF (5 mL) was added slowly, and the reaction solution was further stirred for 4 h. Saturated NH_4Cl aqueous solution (20 mL) was added to quench the reaction. Ethyl acetate (50 mL) was added, and organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was subjected to silica gel chromatography giving the pure products **4.2a-e** and **4.3a-e**, respectively.

trans-4-(1*H*-1,2,3-Benzotriazol-1-yl)-3-benzyl-5-phenyl-1-(4-methoxyphenyl) imidazolidin-2-one (**4.2a**).

white needles (from methylene chloride and hexanes), mp 155–156 °C. Yield: 82%. ^{1}H NMR δ 3.73 (s, 3H), 3.84 (d, *J* = 15.1 Hz, 1H), 4.86 (d, *J* = 15.1 Hz, 1H), 5.29 (d, *J* = 2.1 Hz, 1H), 6.20 (d, *J* = 2.1 Hz, 1H), 6.80 (d, *J* = 9.0 Hz, 2H), 7.08–7.19 (m, 7H), 7.30–7.40 (m, 3H), 7.43–7.45 (m, 5H), 8.08 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR δ 45.4, 55.3, 64.5, 75.5, 109.7, 114.3, 116.3, 120.5, 122.3, 124.6, 125.9, 127.8, 128.2, 128.4, 128.5, 129.1, 129.4, 130.7, 135.1, 137.7, 146.9, 156.2, 156.4. Anal. Calcd for $C_{29}H_{25}N_5O_2$: C, 73.25; H, 5.30; N, 14.73. Found: C, 73.24; H, 5.46; N, 14.69.

Crystal data for **4.2a** (detailed data are shown in Tables 4.3–4.7).

$C_{29}H_{25}N_5O_2$, MW 475.54, orthorhombic, $P2_12_12_1$, $a = 8.419(5)$, $b = 15.655(9)$, $c = 18.395(11)$ Å, V = 2420(2)Å ^{3}, Z = 4, T = -105 °C, F(000) = 1000, μ (MoKα) = 0.085 mm^{-1}, $D_{calcd} = 1.305$ g.cm^{-3}, $2\theta_{max}$ 53° (CCD area detector, 99.4% completeness), wR(F^2) = 0.071 (all 4851 data), R = 0.037 (3510 data with I > 2σI).

trans-4-(1*H*-1,2,3-Benzotriazol-1-yl)-3-benzyl-5-(4-methylphenyl)-1-(4-methoxy phenyl)imidazolidin-2-one (**4.2b**).

dark red needles (from methylene chloride and hexanes), mp 57–58 °C. Yield: 74%. ^{1}H NMR δ 2.30 (s, 3H), 3.74 (s, 3H), 3.83 (d, *J* = 15.1 Hz, 1H), 4.86 (d, *J* = 15.1 Hz, 1H), 5.25 (d, *J* = 2.3 Hz, 1H), 6.19 (d, *J* = 2.3 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 2H), 7.04–7.16 (m, 9H), 7.37–7.45 (m, 5H), 8.08 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 21.1, 45.4, 55.4, 64.3, 75.7, 109.7, 114.3, 114.7, 120.5, 122.3, 124.6, 125.8, 127.8, 128.2, 128.4, 128.5, 130.1, 130.7, 134.6, 135.1, 139.0, 146.9, 156.2, 156.3. HRMS Calcd for $C_{30}H_{27}N_5O_2$: 489.2165. Found: 489.2202.

trans-4-(1*H*-1,2,3-Benzotriazol-1-yl)-3-benzyl-1,5-bis(4-methoxyphenyl) imidazolidin-2-one (**4.2c**).

yellow needles (from methylene chloride and hexanes), mp 55−57 °C. Yield: 80%. ^{1}H NMR δ 3.75 (s, 3H), 3.76 (s, 3H), 3.83 (d, *J* = 15.0 Hz, 1H), 4.87(d, *J* = 15.0 Hz, 1H), 5.23 (d, *J* = 2.4 Hz, 1H), 6.19 (d, *J* = 2.4 Hz, 1H), 6.82 (d, *J* = 8.9 Hz, 4H), 7.07−7.17 (m, 7H), 7.38−7.45 (m, 5H), 8.09 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 45.4, 55.2, 55.3, 64.0, 75.7, 109.7, 114.3, 114.7, 120.5, 122.5, 124.6, 127.2, 127.8, 128.2, 128.4, 128.5, 129.5, 130.7, 130.8, 135.1, 146.9, 156.1, 156.4, 160.0. HRMS Calcd for $C_{30}H_{27}N_5O_3$: 505.2114. Found: 505.2121.

trans-4-(1*H*-1,2,3-Benzotriazol-1-yl)-3-benzyl-5-(4-fluorophenyl)-1-(4-methoxyphenyl)imidazolidin-2-one (**4.2d**).

dark red needles (from methylene chloride and hexanes), mp 68−69°C. Yield: 61%. ^{1}H NMR δ 3.75 (s, 3H), 3.82 (d, *J* = 15.0 Hz, 1H), 4.88 (d, *J* = 15.0 Hz, 1H), 5.27 (d, *J* = 2.6 Hz, 1H), 6.17 (d, *J* = 2.6 Hz, 1H), 6.80−6.86 (m, 2H), 6.97−7.04 (m, 2H), 7.09−7.20 (m, 7H), 7.36−7.49 (m, 5H), 8.08−8.12 (m, 1H); ^{13}C NMR δ 45.5, 55.4, 63.9, 75.4, 109.6, 114.4, 116.5 (d, *J* = 21.6 Hz), 120.6, 122.5, 124.7, 127.7 (d, *J* = 8.1 Hz), 127.9, 128.3, 128.6, 128.7, 130.4, 130.7, 133.4, 135.0, 147.0, 156.0, 156.6, 162.8 (d, *J* = 248.8 Hz). Anal. Calcd for $C_{29}H_{24}FN_5O_2$: C, 70.57; H, 4.90. Found: C, 70.31; H, 4.74.

trans-4-(1*H*-1,2,3-Benzotriazol-1-yl)-3-benzyl-5-(2-furyl)-1-(4-methoxyphenyl) imidazolidin-2-one (**4.2e**).

oil. Yield: 70%. ^{1}H NMR δ 3.78 (s, 3H), 3.87 (d, *J* = 15.2 Hz, 1H), 4.89 (d, *J* = 15.2 Hz, 1H), 5.35 (d, *J* = 2.7 Hz, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 6.27 (dd, *J* = 1.8, 3.2 Hz, 1H), 6.46 (d, *J* = 2.7 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 7.13−7.19 (m, 5H), 7.33−7.46 (m, 6H), 8.07 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 45.5, 55.4, 58.9, 72.6, 109.6, 109.9, 110.7, 114.4, 120.6, 124.1, 124.7, 127.8, 128.2, 128.4, 128.5, 130.1, 130.8, 135.1, 143.6, 146.9, 149.0, 156.0, 157.2. HRMS Calcd for $C_{27}H_{23}N_5O_3$: 465.1801. Found: 465.1811.

trans-4-(1*H*-1,2,3-Benzotriazol-1-yl)-3-benzyl-5-phenyl-1,3-oxazolan-2-one (**4.3a**).

white prisms (from methylene chloride and hexanes), mp 110–112 °C. Yield: 82%. ^{1}H NMR δ 3.86 (d, J = 15.0 Hz, 1H), 4.70 (d, J = 15.0 Hz, 1H), 5.71 (d, J = 2.8 Hz, 1H), 6.37 (d, J = 2.8 Hz, 1H), 7.03–7.06 (m, 2H), 7.11–7.15 (m, 2H), 7.24–7.27 (m, 2H), 7.35–7.53 (m, 7H), 8.07 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 46.1, 76.2, 78.9, 109.3, 120.5, 124.8, 125.0, 128.1, 128.3, 128.6, 128.7, 129.2, 129.5, 130.4, 133.6, 136.0, 146.8, 156.0. HRMS Calcd for $C_{22}H_{19}N_4O_2$: 371.1508 (M+1). Found: 371.1514 (M+1).

trans-4-(1*H*-1,2,3-Benzotriazol-1-yl)-3-benzyl-5-(4-methylphenyl)-1,3-oxazolan-2-one (**4.3b**).

white prisms (from methylene chloride and hexanes), mp 125–127 °C. Yield: 76%. ^{1}H NMR δ 2.36 (s, 3H), 3.84 (d, J = 15.0 Hz, 1H), 4.72 (d, J = 15.0 Hz, 1H), 5.66 (d, J = 3.0 Hz, 1H), 6.36 (d, J = 3.0 Hz, 1H), 7.06–7.21 (m, 9H), 7.45–7.52 (m, 3H), 8.1 0 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ 21.2, 46.2, 76.4, 79.1, 109.4, 120.7, 124.9, 125.1, 128.3, 128.7, 129.9, 133.2, 133.8, 139.8, 156.1. Anal. Calcd for $C_{23}H_{20}N_4O_2$: C, 71.86; H, 5.24. Found: C, 71.78; H, 5.39.

trans-4-(1*H*-1,2,3-Benzotriazol-1-yl)-3-benzyl-5-(4-methoxyphenyl)-1,3-oxazolan-2-one (**4.3c**).

white prisms (from methylene chloride and hexanes), mp 119–120 °C. Yield: 70%. ^{1}H NMR δ 3.81 (s, 3H), 3.83 (d, J = 15.0 Hz, 1H), 4.74 (d, J = 15.0 Hz, 1H), 5.64 (d, J = 2.9 Hz, 1H), 6.36 (d, J = 2.9 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 7.07–7.19 (m, 7H), 7.45–7.54 (m, 3H), 8.09 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ 46.2, 55.4, 76.4, 79.0, 109.4, 114.6, 120.7, 124.9, 126.8, 128.0, 128.3, 128.7, 130.4, 133.9, 147.0, 156.1, 160.5. HRMS Calcd for $C_{23}H_{21}N_4O_3$: 4401.1614 (M+1). Found: 401.1610 (M+1).

trans-4-(1*H*-1,2,3-Benzotriazol-1-yl)-3-benzyl-5-(4-fluorophenyl)-1,3-oxazolan-2-one (**4.3d**).

red prisms (from methylene chloride and hexanes), mp 117–118 °C. Yield: 72%. ^{1}H NMR δ 3.85 (d, *J* = 15.0 Hz, 1H), 4.71 (d, *J* =15.0 Hz, 1H), 5.71 (d, *J* = 2.7 Hz, 1H), 6.34 (d, *J* = 2.7 Hz, 1H), 7.04–7.28 (m, 9H), 7.42–7.54 (m, 3H), 8.07 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 46.1, 76.1, 78.3, 109.2, 116.3 (d, *J* = 22.2 Hz), 120.6, 124.8, 127.1 (d, *J* = 8.5 Hz), 128.1, 128.2, 128.6, 130.3, 131.0, 131.9, 133.6, 146.8, 155.7, 163.1 (d, *J* = 249.0 Hz). Anal. Calcd for $C_{22}H_{17}FN_4O_2$: C, 68.03; H, 4.41; N, 14.42. Found: C, 67.93; H, 4.66; N, 14.02.

trans-4-(1*H*-1,2,3-Benzotriazol-1-yl)-3-benzyl-5-(2-furyl)-1,3-oxazolan-2-one (**4.3e**).

dark red oil. Yield: 66%. ^{1}H NMR δ 3.87 (d, *J* = 15.0 Hz, 1H), 4.77 (d, *J* = 15.0 Hz, 1H), 5.74 (d, *J* = 2.9 Hz, 1H), 6.37 (d, *J* = 2.9 Hz, 1H), 6.44 (d, *J* = 3.0 Hz, 1H), 6.63 (d, *J* = 3.0 Hz, 1H), 7.13–7.22 (m, 5H), 7.40–7.52 (m, 4H), 8.05 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR δ 46.1, 72.5, 72.7, 109.1, 110.8, 111.3, 120.5, 124.8, 127.6, 128.1, 128.6, 128.7, 130.4, 133.6, 144.4, 146.7, 147.1, 155.5. HRMS Calcd for $C_{20}H_{17}N_4O_3$: 361.1301 (M+1). Found: 361.1273 (M+1).

General Procedure for the Synthesis of Compounds **4.5a-g**. Grignard reagent R^2MgBr (2 mmol, 1.0 M in THF) was added to $ZnCl_2$ (2 mmol, 1.0 M in diethyl ether) in THF (10 mL) at 0 °C and the resulting mixture was further stirred at room temperature for 20 min. Then **4.2a-e** (0.4 mmol) in THF (3 mL) was added and the reaction solution was heated under reflux for 12 h. After the solution cooled down to room temperature, saturated NH_4Cl aqueous solution (20 mL) was added and the resulting solution was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was then subjected to silica gel chromatography, and the pure products **4.5a-g** and **4.6** were obtained, respectively.

trans-1-Benzyl-3-(4-methoxyphenyl)-4,5-diphenylimidazolidin-2-one (**4.5a**).

white prisms (from methylene chloride and hexanes), mp 113–114 °C. Yield: 68%. ^{1}H NMR δ 3.69 (s, 3H), 3.70 (d, J = 14.9 Hz, 1H), 4.14 (d, J = 6.6 Hz, 1H), 4.86 (d, J = 6.6 Hz, 1H), 5.07 (d, J = 15.0 Hz, 1H), 6.75 (d, J = 9.0 Hz, 2H), 7.06–7.38 (m, 17H); ^{13}C NMR δ 45.6, 55.3, 65.7, 67.7, 113.8, 122.6, 126.4, 127.3, 127.4, 128.1, 128.5, 128.6, 128.8, 129.0, 132.2, 136.4, 138.3, 139.2, 155.8, 158.4. Anal. Calcd for $C_{29}H_{26}N_2O_2$: C, 80.16; H, 6.03; N, 6.45. Found: C, 79.95; H, 6.18; N, 6.44.

Crystal data for **4.5a** (Detailed data are shown in Tables 4.8–4.12).

$C_{29}H_{26}N_2O_2$, MW 434.52, orthorhombic, Pbca, a = 10.311(3), b = 10.693(3), c = 41.759(11) Å, V = 4602(2)Å^3, Z = 8, T = -105 °C, F(000) = 1840, μ (MoKα) = 0.079 mm^{-1}, D_{calcd} = 1.254 g.cm^{-3}, $2\theta_{max}$ 53° (CCD area detector, 99.2% completeness), wR(F^2) = 0.115 (all 4700 data), R = 0.044 (3347 data with I > 2σI).

trans-1-Benzyl-3-(4-methoxyphenyl)-4-(4-methylphenyl)-5-phenylimidazolidin-2-one (**4.5b**).

white prisms (from methylene chloride and hexanes), mp 135–136 °C. Yield: 50%. ^{1}H NMR δ 2.26 (s, 2H), 3.69 (d, J = 15.7 Hz, 1H), 3.71 (s, 3H), 4.12 (d, J = 6.6 Hz, 1H), 4.82 (d, J = 6.6 Hz, 1H), 5.07 (d, J = 15.7 Hz, 1H), 6.74–6.77 (m, 2H), 6.95 (d, J = 8.2 Hz, 2H), 7.02 (d, J = 7.9 Hz, 2H), 7.13–7.22 (m, 4H), 7.23–7.31 (m, 5H), 7.36–7.38

(m, 3H); ^{13}C NMR δ 21.1, 45.7, 55.3, 65.8, 67.6, 113.8, 122.6, 126.4, 127.3, 128.5, 128.6, 129.0, 129.5, 132.2. 136.2, 136.4, 137.8, 138.4, 155.8, 158.4. Anal. Calcd for $C_{30}H_{28}N_2O_2$: C, 80.33; H, 6.29; N, 6.25. Found: C, 79.95; H, 6.03; N, 6.22.

trans-1-Benzyl-3,4-bis(4-methoxyphenyl)-5-phenylimidazolidin-2-one (**4.5c**).

yellow prisms (from methylene chloride and hexanes), mp 153−154 °C. Yield: 65%. ^{1}H NMR δ 3.70 (d, *J* =15.0 Hz, 1H), 3.71 (s, 3H), 3.72 (s, 3H), 4.12 (d, *J* = 6.8 Hz, 1H), 4.79 (d, *J* = 6.8 Hz, 1H), 5.07 (d, *J* = 15.0 Hz), 6.73−6.77 (m, 4H), 6.98 (d, *J* = 8.6 Hz, 2H), 7.14−7.18 (m, 4H), 7.23−7.29 (m, 5H), 7.29−7.38 (m, 3H); ^{13}C NMR δ 45.7, 55.1, 55.3, 66.0, 67.4, 113.8, 114.2, 122.9, 127.3, 127.4, 127.7, 128.5, 128.5, 129.0, 131.0, 132.2, 136.5, 138.4, 155.9, 158.5, 159.3. Anal. Calcd for $C_{30}H_{28}N_2O_3$: N, 6.03. Found: N, 6.03.

trans-1-Benzyl-4-(4-fluorophenyl)-3-(4-methoxyphenyl)-5-phenylimidazolidin-2-one (**4.5d**).

dark red oil. Yield: 60%. ^{1}H NMR δ 3.70 (d, *J* = 14.8 Hz, 1H), 3.72 (s, 3H), 4.09 (d, *J* = 6.8 Hz, 1H), 4.84 (d, *J* = 6.8 Hz, 1H), 5.06 (d, *J* = 14.8 Hz, 1H), 6.76 (d, *J* = 9.0 Hz, 2H), 6.90 (t, *J* = 8.7 Hz, 2H), 7.00−7.13 (m, 2H), 7.14−7.17 (m, 4H), 7.24−7.28 (m, 5H), 7.37−7.39 (m, 3H); ^{13}C NMR δ 45.7, 55.3, 65.9, 67.3, 114.0, 115.8 (d, *J* = 21.8 Hz), 122.8, 127.3, 127.5, 128.2 (d, *J* = 8.0 Hz), 128.5, 128.6, 128.7, 129.1, 132.0, 134.9, 136.3, 138.0, 156.1, 158.4, 162.4 (d, *J* = 246.8 Hz). Anal. Calcd for $C_{29}H_{25}FN_2O_2$: N, 6.19. Found: N, 6.24.

trans-1-Benzyl-4-(2-furyl)-3-(4-methoxyphenyl)-5-phenylimidazolidin-2-one (**4.5e**).

dark red oil. Yield: 66%. ^{1}H NMR δ 3.74 (d, *J* = 15.1 Hz, 1H), 3.75 (s, 3H), 4.46

(d, *J* = 6.3 Hz, 1H), 4.84 (d, *J* = 6.3 Hz, 1H), 5.09 (d, *J* = 15.1 Hz, 1H), 6.09 (d, *J* = 3.2 Hz, 1H), 6.23 (dd, *J* = 1.9, 3.2 Hz, 1H), 6.80–6.82 (m, 2H), 7.16–7.39 (m, 13H); ^{13}C NMR δ 45.6, 55.4, 62.0, 62.2, 109.1, 110.3, 114.0, 123.8, 127.1, 127.4, 128.4, 128.6, 129.1, 131.7, 136.3, 138.3, 142.9, 150.9, 156.5. HRMS Calcd for $C_{27}H_{24}N_2O_3$: 425.1865 (M+1). Found: 425.1855 (M+1).

trans-1-Benzyl-3-(4-methoxyphenyl)-4-phenyl-5-(2-phenylethynyl)imidazolidin-2-one (**4.5f**).

yellow oil. Yield: 74%. ^{1}H NMR δ 3.71 (s, 3H), 4.14 (d, *J* = 6.6 Hz, 1H), 4.30 (d, *J* = 15.0 Hz, 1H), 5.04 (d, *J* = 15.0 Hz, 1H), 6.77 (d, *J* = 6.6 Hz, 1H), 6.76–6.79 (m, 2H), 7.41–7.45 (m, 17H); ^{13}C NMR δ 46.2, 54.1, 55.3, 64.4, 84.3, 86.9, 113.9, 121.8, 122.9, 126.5, 127.5, 128.4, 128.5, 128.6, 128.9, 129.0, 131.8, 136.4, 138.4, 147.2, 156.1, 157.6. Anal. Calcd for $C_{31}H_{26}N_2O_2$: N, 6.11. Found: N, 6.12.

trans-1-Benzyl-3-(4-methoxyphenyl)-4-phenyl-5-vinylimidazolidin-2-one (**4.5g**).

white prisms (from methylene chloride and hexanes), mp 107–108 °C. Yield: 68%. ^{1}H NMR δ 3.64 (dd, *J* = 7.0, 8.6 Hz, 1H), 3.70 (s, 3H), 4.05 (d, *J* = 15.1 Hz, 1H), 4.73 (d, *J* = 7.0 Hz, 1H), 4.91 (d, *J* = 15.1 Hz, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 5.30 (d, *J* = 10.7 Hz, 1H), 5.82 (ddd, *J* = 8.6 , 10.7, 17.0 Hz, 1H), 6.75 (m, 2H), 7.16–7.29 (m, 12H); ^{13}C NMR δ 45.7, 55.3, 64.9, 65.4, 113.8, 120.8, 122.6, 126.6, 127.3, 128.0, 128.4, 128.5, 128.7, 132.2, 135.1, 136.9, 138.8, 155.8, 158.2. Anal. Calcd for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29. Found: C, 77.59; H, 6.60; N, 7.21.

1-Benzyl-3-(4-methoxyphenyl)-4-phenyl-1,3-dihydro-2*H*-imidazol-2-one (**4.6**).

white needles (from methylene chloride and hexanes), mp 95–96 °C. Yield: 50%. ^{1}H NMR δ 3.79 (s, 3H), 4.90 (s, 2H), 6.32 (s, 1H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.99–7.02

(m, 2H), 7.13–7.17 (m, 5H), 7.34–7.38 (m, 5H); ^{13}C NMR δ 47.3, 55.4, 108.8, 114.2, 124.2, 126.9, 127.2, 127.9, 128.2, 128.3, 128.4, 128.8, 129.4, 136.7, 153.4, 158.4. HRMS Calcd for $C_{23}H_{21}N_2O_2$: 357.1603 (M+1). Found: 357.1601 (M+1).

General Procedure for the Synthesis of Compounds **4.5h-k.** $BF_3 \cdot Et_2O$ (2 mmol) in CH_2Cl_2 (2 mL) was added to **4.2a** or **4.2e** (0.4 mmol) in CH_2Cl_2 (10 mL) at –78 °C. After the reaction mixture was stirred for 30 min, allyltrimethyl silane or a vinyloxytrimethyl silane (2 mmol) was added and the reaction mixture was further stirred for 4 h at this temperature. Then the reaction solution was warmed up to room temperature and stirred overnight. Saturated NH_4Cl aqueous solution (20 mL) was added and extracted by CH_2Cl_2 (3 × 15 mL). Combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was then subjected to silica gel chromatography affording the pure products **4.5h-k**, respectively.

trans-4-Allyl-3-benzyl-1-(4-methoxyphenyl)-5-phenylimidazolidin-2-one (**4.5h**).

white needles (from methylene chloride and hexanes), mp 74–75 °C. Yield: 67%. ^{1}H NMR δ 2.39–2.43 (m, 2H), 3.32–3.37 (m, 1H), 3.71 (s, 3H), 4.15 (d, J = 15.3 Hz, 1H), 4.76 (d, J = 5.1 Hz, 1H), 4.98 (d, J = 15.3 Hz, 1H), 5.20–5.26 (m, 2H), 5.66–5.75 (m, 1H), 6.73–6.78 (m, 2H), 7.17–7.33 (m, 12H); ^{13}C NMR δ 35.8, 45.6, 55.4, 60.4, 62.7, 113.9, 119.6, 122.1, 126.4, 127.4, 127.9, 128.0, 128.6, 128.9, 132.3, 136.9, 140.3, 155.6, 158.0. HRMS Calcd for $C_{26}H_{27}N_2O_2$: 399.2073 (M+1). Found: 399.2071 (M+1).

trans-4-Allyl-3-benzyl-5-(2-furyl)-1-(4-methoxyphenyl)imidazolidin-2-one (**4.5i**).

yellow oil. Yield: 40%. ^{1}H NMR δ 2.38–2.40 (m, 2H), 3.63 (dd, J = 5.2, 10.2 Hz, 1H), 3.75 (*s*, 3H), 4.18 (d, J = 15.5 Hz, 1H), 4.78 (d, J = 5.2 Hz, 1H), 4.97 (d, J = 15.5 Hz, 1H), 5.14 (*s*, 1H), 5.19 (d, J = 5.3 Hz,1H), 5.63–5.72 (m, 1H), 6.11 (d, J = 3.1 Hz, 1H), 6.22 (d, J = 1.7 Hz, 1H), 6.81 (d, J = 9.0 Hz, 2H), 7.23–7.27 (m, 3H), 7.30–7.33 (m, 5H); ^{13}C NMR δ 35.9, 45.6, 55.4, 57.1, 57.3, 108.4, 110.3, 114.0, 119.5, 123.4, 127.4, 128.0, 128.6, 131.9, 136.9, 142.5, 152.0, 156.3, 157.7. Calcd for $C_{24}H_{25}N_2O_3$: 389.1865 (M+1). Found: 389.1828 (M+1).

trans-1-Benzyl-5-(2-oxo-2-phenylethyl)-3-(4-methoxyphenyl)-4-phenylimidazolidin -2-one (**4.5j**).

white needles (from methylene chloride and hexanes), mp 118–119 °C. Yield: 63%. ^{1}H NMR δ 3.21 (dd, J = 8.5, 17.4 Hz, 1H), 3.36 (dd, J = 4.2, 17.4 Hz, 1H), 3.70 (s, 3H), 3.94–3.99 (m, 1H), 4.31 (d, J = 15.4 Hz, 1H), 4.79 (d, J = 15.4 Hz, 1H), 4.85 (d, J = 3.1 Hz), 6.74 (d, J = 9.1 Hz, 2H), 7.20–7.43 (m, 14H), 7.55 (t, J = 7.3 Hz, 1H), 7.78 (d, J = 7.3 Hz, 2H); ^{13}C NMR δ 40.9, 45.9, 55.3, 58.2, 64.3, 113.9, 121.2, 126.3, 127.4, 127.9, 128.0, 128.5, 128.6, 128.8, 132.5, 133.6, 136.2, 137.1, 139.7, 155.4, 157.4, 197.4. Anal. Calcd for $C_{31}H_{28}N_2O_3$: C, 78.13; H, 5.92; N, 5.88. Found: C, 77.73; H, 6.04; N, 5.81.

trans-1-Benzyl-3-(4-methoxyphenyl)-5-(2-oxocyclohexyl)-4-phenylimidazolidin-2-one (**4.5k**).

yellow oil. Yield: 70%. ^{1}H NMR δ 1.26–1.63 (m, 3H), 1.88–2.22 (m, 4H), 2.33–2.38 (m, 1H), 2.52–2.55 (m. 1H), 3.71 (s, 3H), 3.92 (t, J = 3.7 Hz, 1H), 4.25 (d, J = 15.1 Hz, 1H), 4.60 (d, J = 4.0 Hz, 1H), 4.68 (d, J =15.1 Hz, 1H), 6.75(d, J = 9.1 Hz, 2H), 7.13–7.34 (m, 12H). ^{13}C NMR δ 24.7, 26.6, 27.8 (27.1), 42.1, 47.6, 53.9, 55.3, 60.6 (60.1), 64.0, 114.0 (114.2), 122.9 (120.9), 126.2 (125.4), 127.3 (126.9), 128.0 (127.6), 128.3, 128.6, 128.8, 132.2, 137.4, 140.8, 156.0, 158.9, 210.4. HRMS Calcd for $C_{29}H_{31}N_2O_3$: 455.2335 (M+1). Found: 455.2345 (M+1).

Synthesis of *trans*-1-Benzyl-3-(4-methoxyphenyl)-4-phenyl-5-propylimidazolidin-2-one (**4.7**). Compound **4.5h** (0.13 mmol) and p-toluenesulfonohydrazide (1.3 mmol) were dissolved in DME (5 mL) and heated until refluxed, then NaOAc aqueous solution (2.2 mmol, 5 mL) was added within 30 min and the reaction mixture was further heated under reflux for 1 h. The resulting reaction mixture was cooled down to room temperature and water (20 mL) was added. The solution was extracted with ethyl acetate (3 × 20 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was then subjected to silica gel chromatography, and **4.7** was obtained as white prisms (from methylene chloride and hexanes), mp 129–130°C. Yield: 100%. ^{1}H NMR δ 0.87 (t, *J* = 7.3 Hz, 3H), 1.21–1.41 (m, 2H), 1.58–1.64 (m, 2H), 3.25–3.28 (m, 1H), 3.71 (s, 3H), 4.10 (d, *J* = 15.4 Hz, 1H), 4.69 (d, *J* = 4.9 Hz, 1H), 4.95 (d, *J* = 15.4 Hz, 1H), 6.74 (m, *J* = 2.2 Hz, 2H), 7.17–7.32 (m, 12H); ^{13}C NMR δ 14.1, 17.1, 33.7, 45.6, 55.3, 61.0, 63.7, 113.9, 122.0, 126.3, 127.4, 127.9, 128.0, 128.5, 128.9, 132.6, 137.1, 140.9, 155.6, 158.0. Anal. Calcd for $C_{26}H_{28}N_2O_2$: N, 6.99. Found: N, 6.65.

Table 4.3. Crystal Data and Structure Refinement for **4.2a**.

Identification code	3ge	
Empirical formula	C29 H25 N5 O2	
Formula weight	475.54	
Temperature	168(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.419(5) Å	α= 90°.
	B = 15.655(9) Å	β= 90°.
	C = 18.359(11) Å	γ= 90°.
Volume	2420(2) Å^3	
Z	4	
Density (calculated)	1.305 Mg/m^3	
Absorption coefficient	0.085 mm^{-1}	
F(000)	1000	
Crystal size	0.62 x 0.17 x 0.16 mm^3	
Theta range for data collection	2.22 to 26.40°.	
Index ranges	-10<=h<=3, -19<=k<=19, -22<=l<=22	
Reflections collected	10883	
Independent reflections	4851 [R(int) = 0.0263]	
Completeness to theta = 26.40°	99.4 %	
Absorption correction	None	
Max. and min. transmission	0.9866 and 0.9494	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4851 / 0 / 326	
Goodness-of-fit on F^2	0.907	
Final R indices [I>2sigma(I)]	R1 = 0.0366, wR2 = 0.0669	
R indices (all data)	R1 = 0.0578, wR2 = 0.0708	
Absolute structure parameter	0.7(11)	
Largest diff. peak and hole	0.129 and -0.201 e.Å^{-3}	

Table 4.4. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **4.2a**. U(eq) is Defined as One Third of the Trace of the Orthogonalized U^{ij} Tensor.

	X	Y	Z	U(eq)
N(1)	1933(2)	9859(1)	424(1)	27(1)
C(2)	729(2)	9731(1)	914(1)	28(1)
O(2)	671(2)	9203(1)	1404(1)	34(1)
N(3)	-444(2)	10317(1)	762(1)	28(1)
C(4)	-3(2)	10912(1)	203(1)	28(1)
C(5)	1523(2)	10517(1)	-119(1)	26(1)
C(11)	3416(2)	9425(1)	404(1)	26(1)
C(12)	4563(2)	9685(1)	-95(1)	30(1)
C(13)	6005(2)	9275(1)	-131(1)	32(1)
C(14)	6351(2)	8602(1)	329(1)	31(1)
C(15)	5237(2)	8343(1)	830(1)	37(1)
C(16)	3772(2)	8746(1)	864(1)	36(1)
O(1)	7823(2)	8243(1)	245(1)	41(1)
C(17)	8232(2)	7567(1)	730(1)	48(1)
C(30)	-1882(2)	10389(1)	1203(1)	34(1)
C(31)	-1696(2)	11011(1)	1827(1)	28(1)
C(32)	-696(2)	10821(1)	2402(1)	35(1)
C(33)	-432(2)	11409(1)	2952(1)	43(1)
C(34)	-1192(2)	12190(1)	2935(1)	42(1)
C(35)	-2217(2)	12378(1)	2372(1)	41(1)
C(36)	-2467(2)	11794(1)	1816(1)	36(1)
N(41)	225(2)	11783(1)	475(1)	29(1)
N(42)	-731(2)	12402(1)	199(1)	41(1)
N(43)	-354(2)	13130(1)	496(1)	46(1)
C(43A)	874(2)	12993(1)	977(1)	34(1)
C(44)	1677(2)	13568(1)	1426(1)	45(1)
C(45)	2844(3)	13246(1)	1859(1)	48(1)
C(46)	3213(2)	12366(1)	1855(1)	46(1)
C(47)	2432(2)	11794(1)	1416(1)	37(1)
C(47A)	1255(2)	12128(1)	974(1)	28(1)
C(51)	1223(2)	10158(1)	-873(1)	25(1)
C(52)	1913(2)	10544(1)	-1472(1)	33(1)
C(53)	1559(2)	10266(1)	-2173(1)	36(1)
C(54)	484(2)	9610(1)	-2269(1)	39(1)
C(55)	-185(2)	9213(1)	-1673(1)	40(1)
C(56)	187(2)	9476(1)	-979(1)	33(1)

Table 4.5. Bond Lengths [Å] and Angles [°] for **4.2a**.

N(1)-C(2)	1.370(2)
N(1)-C(11)	1.422(2)
N(1)-C(5)	1.474(2)
C(2)-O(2)	1.222(2)
C(2)-N(3)	1.377(2)
N(3)-C(4)	1.435(2)
N(3)-C(30)	1.460(2)
C(4)-N(41)	1.464(2)
C(4)-C(5)	1.544(2)
C(5)-C(51)	1.516(2)
C(11)-C(16)	1.391(2)
C(11)-C(12)	1.391(2)
C(12)-C(13)	1.376(2)
C(13)-C(14)	1.381(2)
C(14)-O(1)	1.369(2)
C(14)-C(15)	1.375(3)
C(15)-C(16)	1.387(3)
O(1)-C(17)	1.425(2)
C(30)-C(31)	1.511(2)
C(31)-C(32)	1.382(2)
C(31)-C(36)	1.388(3)
C(32)-C(33)	1.383(3)
C(33)-C(34)	1.380(3)
C(34)-C(35)	1.378(3)
C(35)-C(36)	1.386(3)
N(41)-N(42)	1.358(2)
N(41)-C(47A)	1.372(2)
N(42)-N(43)	1.303(2)
N(43)-C(43A)	1.376(2)
C(43A)-C(47A)	1.392(2)
C(43A)-C(44)	1.395(3)
C(44)-C(45)	1.361(3)
C(45)-C(46)	1.411(3)
C(46)-C(47)	1.374(3)
C(47)-C(47A)	1.383(3)
C(51)-C(52)	1.384(2)
C(51)-C(56)	1.392(2)
C(52)-C(53)	1.390(3)
C(53)-C(54)	1.380(3)
C(54)-C(55)	1.378(3)
C(55)-C(56)	1.376(3)
C(2)-N(1)-C(11)	126.68(15)
C(2)-N(1)-C(5)	111.92(14)

Table 4.5—Continued.

C(11)-N(1)-C(5)	121.40(14)
O(2)-C(2)-N(1)	127.72(16)
O(2)-C(2)-N(3)	124.84(16)
N(1)-C(2)-N(3)	107.44(15)
C(2)-N(3)-C(4)	113.11(14)
C(2)-N(3)-C(30)	122.22(15)
C(4)-N(3)-C(30)	124.12(14)
N(3)-C(4)-N(41)	113.29(15)
N(3)-C(4)-C(5)	103.23(13)
N(41)-C(4)-C(5)	113.24(14)
N(1)-C(5)-C(51)	113.41(14)
N(1)-C(5)-C(4)	102.46(13)
C(51)-C(5)-C(4)	111.10(14)
C(16)-C(11)-C(12)	118.34(16)
C(16)-C(11)-N(1)	122.54(16)
C(12)-C(11)-N(1)	119.12(15)
C(13)-C(12)-C(11)	120.45(16)
C(12)-C(13)-C(14)	120.91(17)
O(1)-C(14)-C(15)	124.86(17)
O(1)-C(14)-C(13)	115.84(17)
C(15)-C(14)-C(13)	119.30(18)
C(14)-C(15)-C(16)	120.21(17)
C(15)-C(16)-C(11)	120.77(18)
C(14)-O(1)-C(17)	116.94(15)
N(3)-C(30)-C(31)	112.56(14)
C(32)-C(31)-C(36)	118.99(17)
C(32)-C(31)-C(30)	120.26(16)
C(36)-C(31)-C(30)	120.68(18)
C(31)-C(32)-C(33)	120.85(18)
C(34)-C(33)-C(32)	119.9(2)
C(35)-C(34)-C(33)	119.71(19)
C(34)-C(35)-C(36)	120.46(19)
C(35)-C(36)-C(31)	120.07(19)
N(42)-N(41)-C(47A)	110.05(14)
N(42)-N(41)-C(4)	117.37(15)
C(47A)-N(41)-C(4)	132.57(14)
N(43)-N(42)-N(41)	108.90(16)
N(42)-N(43)-C(43A)	108.33(15)
N(43)-C(43A)-C(47A)	108.81(17)
N(43)-C(43A)-C(44)	129.92(17)
C(47A)-C(43A)-C(44)	121.26(18)
C(45)-C(44)-C(43A)	117.09(18)
C(44)-C(45)-C(46)	121.13(19)

Table 4.5—Continued.

C(47)-C(46)-C(45)	122.4(2)
C(46)-C(47)-C(47A)	116.09(18)
N(41)-C(47A)-C(47)	134.04(16)
N(41)-C(47A)-C(43A)	103.89(16)
C(47)-C(47A)-C(43A)	122.07(18)
C(52)-C(51)-C(56)	119.16(17)
C(52)-C(51)-C(5)	119.64(15)
C(56)-C(51)-C(5)	121.08(16)
C(51)-C(52)-C(53)	120.60(17)
C(54)-C(53)-C(52)	119.49(18)
C(55)-C(54)-C(53)	120.11(18)
C(56)-C(55)-C(54)	120.55(18)
C(55)-C(56)-C(51)	120.03(18)

Table 4.6. Anisotropic Displacement Parameters ($\mathrm{Å}^2 \times 10^3$) for **4.2a**. The Anisotropic Displacement Factor Exponent Takes the Form: $-2\pi^2[\, h^2a^{*2}U^{11} + \ldots + 2\, h\, k\, a^*\, b^*\, U^{12}\,]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	26(1)	29(1)	25(1)	5(1)	2(1)	5(1)
C(2)	31(1)	28(1)	25(1)	-3(1)	0(1)	-3(1)
O(2)	41(1)	31(1)	30(1)	5(1)	8(1)	0(1)
N(3)	28(1)	28(1)	29(1)	0(1)	6(1)	1(1)
C(4)	28(1)	29(1)	27(1)	-4(1)	-3(1)	2(1)
C(5)	27(1)	24(1)	27(1)	2(1)	2(1)	0(1)
C(11)	25(1)	26(1)	26(1)	-2(1)	-3(1)	2(1)
C(12)	29(1)	28(1)	32(1)	6(1)	-3(1)	1(1)
C(13)	27(1)	33(1)	35(1)	3(1)	2(1)	-2(1)
C(14)	28(1)	30(1)	36(1)	-4(1)	-5(1)	3(1)
C(15)	39(1)	36(1)	35(1)	9(1)	-2(1)	9(1)
C(16)	37(1)	38(1)	32(1)	10(1)	3(1)	2(1)
O(1)	32(1)	45(1)	46(1)	7(1)	0(1)	13(1)
C(17)	49(1)	47(1)	49(1)	8(1)	-4(1)	22(1)
C(30)	28(1)	40(1)	33(1)	-6(1)	5(1)	-5(1)
C(31)	22(1)	32(1)	32(1)	-4(1)	7(1)	-2(1)
C(32)	35(1)	35(1)	35(1)	-2(1)	4(1)	2(1)
C(33)	40(1)	54(1)	34(1)	-11(1)	-4(1)	4(1)
C(34)	47(1)	38(1)	40(1)	-16(1)	9(1)	-7(1)
C(35)	51(1)	29(1)	42(1)	-2(1)	13(1)	5(1)
C(36)	34(1)	40(1)	33(1)	4(1)	5(1)	3(1)
N(41)	29(1)	26(1)	31(1)	2(1)	-1(1)	6(1)
N(42)	44(1)	36(1)	43(1)	2(1)	-8(1)	14(1)
N(43)	55(1)	30(1)	55(1)	-3(1)	-7(1)	12(1)
C(43A)	33(1)	29(1)	40(1)	0(1)	3(1)	3(1)
C(44)	48(1)	28(1)	58(2)	-6(1)	3(1)	-2(1)
C(45)	46(1)	38(1)	59(2)	-11(1)	-4(1)	-10(1)
C(46)	36(1)	46(1)	56(2)	-3(1)	-15(1)	-1(1)
C(47)	35(1)	32(1)	45(1)	-1(1)	-5(1)	1(1)
C(47A)	25(1)	28(1)	30(1)	2(1)	4(1)	-1(1)
C(51)	24(1)	25(1)	26(1)	-2(1)	2(1)	4(1)
C(52)	35(1)	31(1)	32(1)	-1(1)	1(1)	-3(1)
C(53)	43(1)	39(1)	26(1)	1(1)	4(1)	2(1)
C(54)	40(1)	47(1)	29(1)	-12(1)	-4(1)	3(1)
C(55)	36(1)	41(1)	43(1)	-14(1)	1(1)	-6(1)
C(56)	29(1)	36(1)	33(1)	-4(1)	6(1)	-4(1)

Table 4.7. Hydrogen Coordinates (x10^4) and Isotropic Displacement Parameters (Å^{2}x10^3) for **4.2a**.

	x	y	z	U(eq)
H(4A)	-846	10918	-180	34
H(5A)	2382	10958	-140	32
H(12A)	4347	10150	-413	36
H(13A)	6774	9457	-476	38
H(15A)	5472	7888	1155	44
H(16A)	3002	8556	1206	43
H(17A)	8178	7773	1234	73
H(17B)	9313	7370	625	73
H(17C)	7486	7092	666	73
H(30A)	-2156	9819	1400	40
H(30B)	-2771	10578	889	40
H(32B)	-185	10281	2420	42
H(33A)	271	11275	3340	51
H(34A)	-1009	12596	3310	50
H(35A)	-2756	12911	2366	49
H(36A)	-3167	11931	1427	43
H(44A)	1421	14159	1429	54
H(45A)	3420	13619	2170	57
H(46A)	4030	12163	2167	55
H(47A)	2685	11202	1415	45
H(52A)	2636	11003	-1405	39
H(53A)	2052	10525	-2582	43
H(54A)	205	9432	-2747	47
H(55A)	-908	8755	-1743	48
H(56A)	-265	9192	-571	39

Table 4.8. Crystal Data and Structure Refinement for **4.5a**.

Identification code	3gc	
Empirical formula	C29 H26 N2 O2	
Formula weight	434.52	
Temperature	168(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 10.311(3) Å	α= 90°.
	B = 10.693(3) Å	β= 90°.
	C = 41.759(11) Å	γ = 90°.
Volume	4604(2) Å^3	
Z	8	
Density (calculated)	1.254 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	1840	
Crystal size	0.75 x 0.69 x 0.26 mm^3	
Theta range for data collection	1.95 to 26.44°.	
Index ranges	-5<=h<=12, -13<=k<=11, -52<=l<=52	
Reflections collected	29788	
Independent reflections	4700 [R(int) = 0.0361]	
Completeness to theta = 26.44°	99.2 %	
Absorption correction	None	
Max. and min. transmission	0.9798 and 0.9432	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4700 / 0 / 299	
Goodness-of-fit on F^2	1.029	
Final R indices [I>2sigma(I)]	R1 = 0.0435, wR2 = 0.1064	
R indices (all data)	R1 = 0.0668, wR2 = 0.1148	
Largest diff. peak and hole	0.208 and -0.218 e.Å^{-3}	

Table 4.9. Atomic Coordinates (x10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$x 10^3) for **4.5a**. U(eq) is Defined as One Third of the Trace of the Orthogonalized U^{ij} Tensor.

	x	y	z	U(eq)
N(1)	5511(1)	808(1)	1068(1)	32(1)
C(2)	4398(1)	939(2)	1256(1)	33(1)
O(2)	3732(1)	1877(1)	1280(1)	40(1)
N(3)	4230(1)	-165(1)	1414(1)	35(1)
C(4)	5112(1)	-1138(2)	1302(1)	32(1)
C(5)	6217(1)	-321(1)	1161(1)	31(1)
C(11)	5964(1)	1652(1)	834(1)	30(1)
C(12)	5131(2)	2503(2)	686(1)	36(1)
C(13)	5597(2)	3314(2)	456(1)	39(1)
C(14)	6897(2)	3295(2)	367(1)	35(1)
C(15)	7716(2)	2428(2)	503(1)	36(1)
C(16)	7252(1)	1611(2)	736(1)	33(1)
O(1)	7258(1)	4172(1)	142(1)	48(1)
C(17)	8600(2)	4327(2)	87(1)	55(1)
C(30)	3067(2)	-481(2)	1595(1)	38(1)
C(31)	3398(2)	-1138(2)	1906(1)	38(1)
C(32)	4436(2)	-743(2)	2096(1)	54(1)
C(33)	4743(2)	-1374(2)	2378(1)	66(1)
C(34)	4016(2)	-2382(2)	2475(1)	67(1)
C(35)	2994(2)	-2784(2)	2290(1)	60(1)
C(36)	2691(2)	-2168(2)	2006(1)	45(1)
C(41)	4506(1)	-2027(1)	1061(1)	31(1)
C(42)	4592(2)	-3299(2)	1113(1)	38(1)
C(43)	4106(2)	-4144(2)	893(1)	45(1)
C(44)	3537(2)	-3716(2)	614(1)	46(1)
C(45)	3428(2)	-2446(2)	561(1)	43(1)
C(46)	3894(2)	-1602(2)	784(1)	37(1)
C(51)	7288(1)	-74(1)	1405(1)	30(1)
C(52)	8342(2)	-882(2)	1418(1)	38(1)
C(53)	9302(2)	-729(2)	1647(1)	48(1)
C(54)	9226(2)	246(2)	1863(1)	52(1)
C(55)	8198(2)	1060(2)	1850(1)	48(1)
C(56)	7225(2)	902(2)	1624(1)	39(1)

Table 4.10. Bond Lengths [Å] and Angles [°] for **4.5a**.

N(1)-C(2)	1.3969(19)
N(1)-C(11)	1.4092(19)
N(1)-C(5)	1.4625(19)
C(2)-O(2)	1.2201(18)
C(2)-N(3)	1.363(2)
N(3)-C(30)	1.4573(19)
N(3)-C(4)	1.4590(19)
C(4)-C(41)	1.517(2)
C(4)-C(5)	1.552(2)
C(5)-C(51)	1.527(2)
C(11)-C(16)	1.390(2)
C(11)-C(12)	1.397(2)
C(12)-C(13)	1.380(2)
C(13)-C(14)	1.391(2)
C(14)-O(1)	1.3766(19)
C(14)-C(15)	1.378(2)
C(15)-C(16)	1.393(2)
O(1)-C(17)	1.414(2)
C(30)-C(31)	1.518(2)
C(31)-C(36)	1.385(2)
C(31)-C(32)	1.396(2)
C(32)-C(33)	1.394(3)
C(33)-C(34)	1.374(3)
C(34)-C(35)	1.376(3)
C(35)-C(36)	1.391(3)
C(41)-C(42)	1.380(2)
C(41)-C(46)	1.396(2)
C(42)-C(43)	1.383(2)
C(43)-C(44)	1.381(2)
C(44)-C(45)	1.381(3)
C(45)-C(46)	1.381(2)
C(51)-C(52)	1.389(2)
C(51)-C(56)	1.390(2)
C(52)-C(53)	1.387(2)
C(53)-C(54)	1.378(3)
C(54)-C(55)	1.373(3)
C(55)-C(56)	1.388(2)
C(2)-N(1)-C(11)	126.71(13)
C(2)-N(1)-C(5)	110.05(12)
C(11)-N(1)-C(5)	123.15(12)
O(2)-C(2)-N(3)	126.86(14)
O(2)-C(2)-N(1)	126.28(15)
N(3)-C(2)-N(1)	106.82(13)

Table 4.10—Continued.

C(2)-N(3)-C(30)	123.77(13)
C(2)-N(3)-C(4)	112.58(12)
C(30)-N(3)-C(4)	120.89(13)
N(3)-C(4)-C(41)	113.71(12)
N(3)-C(4)-C(5)	100.21(12)
C(41)-C(4)-C(5)	113.83(12)
N(1)-C(5)-C(51)	113.22(12)
N(1)-C(5)-C(4)	101.53(11)
C(51)-C(5)-C(4)	112.03(12)
C(16)-C(11)-C(12)	118.53(14)
C(16)-C(11)-N(1)	120.05(13)
C(12)-C(11)-N(1)	121.35(13)
C(13)-C(12)-C(11)	120.26(14)
C(12)-C(13)-C(14)	120.83(15)
O(1)-C(14)-C(15)	125.04(14)
O(1)-C(14)-C(13)	115.64(14)
C(15)-C(14)-C(13)	119.31(15)
C(14)-C(15)-C(16)	120.06(14)
C(11)-C(16)-C(15)	120.92(15)
C(14)-O(1)-C(17)	117.17(13)
N(3)-C(30)-C(31)	111.53(13)
C(36)-C(31)-C(32)	118.26(17)
C(36)-C(31)-C(30)	120.57(15)
C(32)-C(31)-C(30)	121.15(16)
C(33)-C(32)-C(31)	120.36(19)
C(34)-C(33)-C(32)	120.5(2)
C(33)-C(34)-C(35)	119.7(2)
C(34)-C(35)-C(36)	120.2(2)
C(31)-C(36)-C(35)	121.02(18)
C(42)-C(41)-C(46)	118.77(15)
C(42)-C(41)-C(4)	119.08(14)
C(46)-C(41)-C(4)	122.12(14)
C(41)-C(42)-C(43)	121.03(15)
C(44)-C(43)-C(42)	119.85(17)
C(45)-C(44)-C(43)	119.75(16)
C(44)-C(45)-C(46)	120.36(16)
C(45)-C(46)-C(41)	120.20(15)
C(52)-C(51)-C(56)	118.56(14)
C(52)-C(51)-C(5)	118.97(14)
C(56)-C(51)-C(5)	122.42(13)
C(53)-C(52)-C(51)	120.77(16)
C(54)-C(53)-C(52)	119.95(16)
C(55)-C(54)-C(53)	119.93(16)

Table 4.10—Continued.

C(54)-C(55)-C(56)	120.41(17)
C(55)-C(56)-C(51)	120.38(16)

Table 4.11. Anisotropic Displacement Parameters ($Å^2$x 10^3) for **4.5a**. The Anisotropic Displacement Factor Exponent Takes the Form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	29(1)	33(1)	36(1)	4(1)	5(1)	3(1)
C(2)	28(1)	39(1)	32(1)	-3(1)	2(1)	1(1)
O(2)	35(1)	39(1)	47(1)	-1(1)	6(1)	7(1)
N(3)	32(1)	35(1)	38(1)	-1(1)	9(1)	0(1)
C(4)	30(1)	32(1)	33(1)	0(1)	1(1)	0(1)
C(5)	29(1)	32(1)	32(1)	-2(1)	3(1)	2(1)
C(11)	29(1)	32(1)	29(1)	-4(1)	-1(1)	-2(1)
C(12)	28(1)	43(1)	37(1)	2(1)	0(1)	1(1)
C(13)	37(1)	43(1)	38(1)	5(1)	-5(1)	4(1)
C(14)	40(1)	40(1)	27(1)	2(1)	-1(1)	-7(1)
C(15)	29(1)	46(1)	34(1)	-4(1)	2(1)	-5(1)
C(16)	29(1)	39(1)	32(1)	-1(1)	-1(1)	2(1)
O(1)	44(1)	60(1)	41(1)	15(1)	-1(1)	-10(1)
C(17)	47(1)	71(1)	48(1)	15(1)	5(1)	-16(1)
C(30)	31(1)	45(1)	39(1)	0(1)	8(1)	-3(1)
C(31)	37(1)	46(1)	32(1)	-6(1)	8(1)	0(1)
C(32)	56(1)	67(1)	40(1)	-8(1)	1(1)	-11(1)
C(33)	67(1)	95(2)	35(1)	-8(1)	-7(1)	-3(1)
C(34)	77(2)	88(2)	37(1)	9(1)	4(1)	11(1)
C(35)	67(1)	64(1)	50(1)	14(1)	9(1)	0(1)
C(36)	43(1)	51(1)	42(1)	3(1)	6(1)	-2(1)
C(41)	25(1)	36(1)	33(1)	-2(1)	4(1)	0(1)
C(42)	35(1)	37(1)	41(1)	0(1)	-3(1)	1(1)
C(43)	48(1)	37(1)	51(1)	-6(1)	-5(1)	0(1)
C(44)	41(1)	50(1)	48(1)	-14(1)	-4(1)	-6(1)
C(45)	36(1)	57(1)	36(1)	2(1)	-5(1)	-4(1)
C(46)	34(1)	38(1)	40(1)	5(1)	-2(1)	-1(1)
C(51)	29(1)	30(1)	32(1)	2(1)	3(1)	-3(1)
C(52)	35(1)	33(1)	48(1)	0(1)	0(1)	0(1)
C(53)	36(1)	44(1)	65(1)	14(1)	-10(1)	-2(1)
C(54)	48(1)	66(1)	42(1)	14(1)	-14(1)	-16(1)
C(55)	53(1)	55(1)	36(1)	-8(1)	3(1)	-13(1)
C(56)	36(1)	39(1)	41(1)	-4(1)	5(1)	-2(1)

Table 4.12. Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters (Å^{2}x 10 ^{3}) for **4.5a**.

	x	y	z	U(eq)
H(4A)	5447	-1623	1489	38
H(5A)	6589	-734	966	37
H(12A)	4239	2523	743	43
H(13A)	5022	3892	357	47
H(15A)	8597	2386	438	43
H(16A)	7824	1018	830	40
H(17A)	8736	5020	-63	83
H(17B)	8957	3556	-5	83
H(17C)	9039	4511	289	83
H(30A)	2507	-1031	1463	46
H(30B)	2576	293	1642	46
H(32A)	4936	-39	2032	65
H(33A)	5459	-1106	2503	79
H(34A)	4219	-2799	2670	81
H(35A)	2495	-3485	2356	73
H(36A)	1988	-2457	1879	54
H(42A)	4992	-3598	1303	45
H(43A)	4163	-5016	934	55
H(44A)	3222	-4293	460	55
H(45A)	3031	-2151	370	51
H(46A)	3798	-730	748	45
H(52A)	8406	-1547	1268	46
H(53A)	10011	-1295	1656	58
H(54A)	9885	353	2019	62
H(55A)	8152	1735	1998	58
H(56A)	6513	1465	1619	46

CHAPTER 5
A FACILE ROUTE TO 2-SUBSTITUTED *N*-BOC PYRROLIDINES

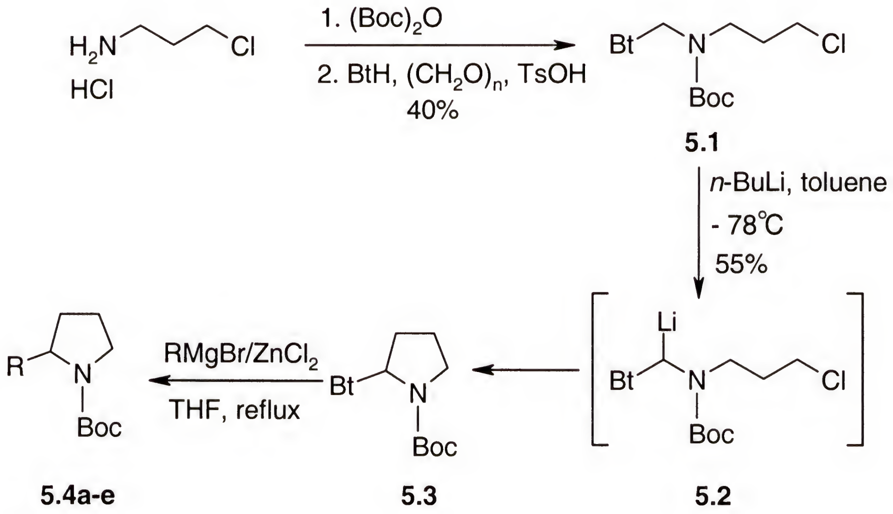
5.1 Introduction

Numerous pyrrolidines are of biological importance [99JOC498, 99JOC5166, 00JMC342, 00JMC984, 00JMC1041, 00JA8635, 00JMC3428, 00JOC2048] and the development of versatile methods for their preparation has shown much recent activity [99JOC498, 99JOC5166, 00JMC342, 00JMC984, 00JMC1041, 00JA8635, 00JMC3428, 00JOC2048, 99JOC1979, 99JOC3763, 99JOC4282, 00JA4821, 00JA5212, 00OL667, 00OL1589].

2-Substituted-*N*-Boc-pyrrolidines have been prepared by two general methods: (i) by direct electrophilic substitution at the 2-position of the *N*-Boc-pyrrolidine ring [91JA9708, 94JA3231, 97JOC7726] and (ii) by intramolecular cyclization of arylmethyl- or allyl-(3-chloropropyl)-*N*-Boc-amines by treatment with *s*-BuLi or *n*-BuLi [96JA715, 99JOC1106]. In this chapter, we report a third approach by nucleophilic displacement of the benzotriazole moiety from *N*-Boc-pyrrolidine **5.3** (which is easily available from the dipole-stabilized carbanion intermediate **5.2** generated from *N*-Boc-*N*-(3-halopropyl)-(benzotriazol-1-ylmethyl)amine **5.1**, Scheme 5.1): a single previous example related to present approach utilizes 2-methoxy-*N*-Boc-pyrrolidine prepared by electromethoxylation of *N*-Boc protected pyrrolidine [97JCS(P1)2163].

5.2 Results and Discussion

Starting material **5.1** was prepared in two steps in 40% overall yield (Scheme 5.1). Protection of 3-chloropropylamine hydrochloride with $(Boc)_2O$ in the presence of Et_3N gave *N*-Boc-3-chloropropylamine [98T15199], which reacted further (without purification) with benzotriazole and paraformaldehyde in the presence of *p*-TsOH in refluxing toluene with azeotropic removal of water to give *N*-Boc-*N*-(benzotriazol-1-ylmethyl)-3-chloropropyl amine (**5.1**). The reaction conditions were optimized for the cyclization of compound **5.1** to compound **5.3**: the best solvent was toluene; others gave a complex reaction mixture (such as THF) or low yields (16% in Et_2O). The best base



Entry	Prod.	R	Yield (%)
1	**5.4a**	Ph	86
2	**5.4b**	4-Me-C_6H_4	66
3	**5.4c**	4-MeO-C_6H_4	70
4	**5.4d**	4-Cl-C_6H_4	62
5	**5.4e**	Ph-C≡C	77

Scheme 5.1

was *n*-BuLi which (1.5 equivalents) was preferred to *s*-BuLi and *t*-BuLi for the cyclization. Compound **5.3** was thus formed *via* intramolecular cyclization in 55% yield.

Treatment of the benzotriazole derivative **5.3** with organozinc reagents gave compounds **5.4a-e** in good to excellent yields (Scheme 5.1). Arylzinc reagents and an alkynylzinc reagent all afforded the corresponding desired products. However, when alkylzinc reagents were used, no desired products but new types of compounds were produced (these results will be discussed in detail in Chapter 6); when allyltrimethylsilane or vinyloxytrimethylsilane were used as nucleophiles to carry out this reaction in the presence of a Lewis acid ($BF_3 \cdot Et_2O$ or $SnCl_4$), no desired products were obtained.

5.3 Conclusion

In conclusion, a general method using *N*-Boc-*N*-(3-halopropyl)(benzotriazol-1-ylmethyl)amine as the starting material is proposed for the preparation of 2-substituted-*N*-Boc-pyrrolidines in good to excellent yields. In the cyclization step, the benzotriazole moiety assists the dipole stabilization in the formation of a carbanion intermediate to make the lithiation regiospecific.

5.4 Experimental Section

General Comments. Melting points were determined on a hot stage apparatus and are uncorrected. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ with TMS as the internal reference. THF was distilled from sodium/benzophenone and CH_2Cl_2 was distilled from CaH_2 under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under argon atmosphere.

Synthesis of *tert*-Butyl *N*-(1*H*-1,2,3-benzotriazol-1-ylmethyl)-*N*-(3-chloropropyl) carbamate (**5.1**). At 0°C, 3-chloropropylamine hydrochloride (1.64g, 12.5 mmol) and Na_2CO_3 (1.33g, 12.5 mmol) were added to the mixed solution of CH_2Cl_2 (40 mL) and saturated brine (30 mL), then stirred for about ten minutes. Di-*tert*-butyl dicarbonate (2.73g, 12.5 mmol) was added into the above solution and the mixed solution was stirred overnight. CH_2Cl_2 (60 mL) was added, then organic layer was separated, dried and evaporated under reduced pressure. The crude product obtained was directly used in next step without purification.

The crude product, prepared as shown above, benzotriazole (1.64g, 13.8 mmol), paraformaldehyde (0.56g, 18.8 mmol) and a catalytic amount of *p*-toluenesulfonic acid were mixed in toluene (150 mL) and refluxed overnight with a Dean-Stark trap to remove the water formed. After toluene was removed under reduced pressure, the crude product was subjected directly to silica gel column chromatography, and product **5.1** was obtained as a colorless sticky oil (which became colorless solid at room temperature) mp 62.5–63.5 °C. Yield: 40%. ^{1}H NMR δ 1.50 (s, 7H), 1.59 (s, 2H), 1.85–1.94 (m, 2H), 3.44–3.49 (m, 4H), 6.15 (s, 2H), 7.39 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ 28.2, 31.0, 41.9, 43.7, 58.6, 81.5, 110.9, 119.6, 124.2, 127.8, 132.2, 146.2, 155.1. Anal. Calcd for $C_{15}H_{21}ClN_4O_2$: C, 55.47; H, 6.52; N, 17.25. Found: C, 55.48; H, 6.71; N, 17.26.

Synthesis of *tert*-Butyl 2-(1*H*-1,2,3-benzotriazol-1-yl)-1-pyrrolidinecarboxylate (**5.3**). At –78 ^{0}C, *n*-BuLi (6 mmol, 1.56M in hexanes) was added slowly to compound **5.1** (1.31g, 4 mmol) in toluene (40 mL), then the solution was further stirred for 5h at this temperature. The reaction was quenched with saturated NH_4Cl aqueous solution and organic layer was separated. The aqueous layer was extracted with ethyl acetate (30 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography and product **5.3** was obtained as a yellow oil. Yield: 55%. ^1H NMR δ 1.09 (s, 4H), 1.41 (s, 5H), 2.02–2.20 (m, 1H), 2.22–2.74 (m, 3H), 3.50–3.95 (m, 2H), 6.57–6.62 (m, 1H), 7.27–7.39 (m, 1H), 7.41–7.54 (m, 1H), 7.81–7.89 (m, 1H), 8.01–8.09 (m, 1H); ^{13}C NMR (two rotomers) 22.6 (23.7), 28.0 (28.2), 34.4 (33.0), 46.8, 71.3 (70.3), 80.6 (80.9), 109.7 (110.4), 119.9 (119.5), 123.8,127.2 (126.2), 131.7 (132.8), 145.6, 153.1(154.1). Anal. Calcd for $C_{15}H_{20}N_4O_2$: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.02; H, 7.34; N, 19.41.

General Procedure for the Synthesis of Compounds **5.4a-e**. To a solution of $ZnCl_2$ (2.5 mmol, 1.0 M in Et_2O) in THF (10 mL) was added RMgBr (2.5 mmol) at 0 °C, then the solution was warmed to room temperature and stirred further for about 20 mins. Compound **5.3** (0.5 mmol) in THF (10 mL) was added to the above prepared solution of organozinc reagent, then the mixed solution was refluxed for 12 h. The was solution cooled down to room temperature and dilute ammonium aqueous solution was added. Then the organic layer was separated and aqueous solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. The solvents were evaporated in vacuo and the residue was subjected to silica gel chromatography to give the product **5.4a**-**e**.

N-(*tert*-Butoxycarbonyl)-2-phenylpyrrolidine (**5.4a**) [97JOC7726].

Oil. Yield: 86%. ^1H NMR δ 1.18 (s, 6H), 1.45 (s, 3H), 1.77–1.92 (m, 3H), 2.22–2.48 (m, 1H), 3.42–3.68 (m, 2H), 4.75 and 4.96 (2 br s, 1H), 7.14–7.20 (m, 3H), 7.22–7.31 (m, 2H); ^{13}C NMR 23.5, 28.4 (28.7), 36.3 (35.1), 47.4, 61.6 (61.0), 79.5, 125.8, 126.8 (127.8), 128.4 (129.7), 145.5 (144.3), 154.9.

N-(*tert*-Butoxycarbonyl)-2-(4-methylphenyl)pyrrolidine (**5.4b**) [97JOC7726].

Oil. Yield: 66%. ^{1}H NMR δ 1.20 (s, 6H), 1.45 (s, 3H), 1.80–1.95 (m, 3H), 2.32 (br s, 4H), 3.43–3.65 (m, 2H), 4.75 and 4.93 (2 br s, 1H), 7.01–7.11 (m, 4H); ^{13}C NMR 21.0 (20.4), 23.1 (23.6), 28.1 (28.7), 35.9 (34.9), 47.0 (47.5), 61.0 (60.5), 79.3, 125.4, 128.7 (129.0), 135.9, 141.9, 154.1 (154.8).

N-(*tert*-Butoxycarbonyl)-2-(4-methoxyphenyl)pyrrolidine (**5.4c**) [97JOC7726].

Oil. Yield: 70%. ^{1}H NMR δ 1.21 (s, 6H), 1.45 (s, 3H), 1.74–1.95 (m, 3H), 2.18–2.36 (m, 1H), 3.44–3.68 (m, 2H), 3.79 (s, 3H), 4.73 and 4.90 (2 br s, 1H), 6.83 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 23.1, 28.2, 35.9, 47.0, 55.2, 60.7, 79.3, 113.5, 114.7, 126.5, 137.4, 158.2.

N-(*tert*-Butoxycarbonyl)-2-(4-chlorophenyl)pyrrolidine (**5.4d**).

Oil. Yield: 62%. ^{1}H NMR δ 1.20 (s, 6H), 1.45 (s, 3H), 1.71–1.92 (m, 3H), 2.20–2.38 (m, 1H), 3.45–3.43 (m, 2H), 4.74 and 4.90 (2 br s, 1H), 7.10 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H); ^{13}C NMR 23.1 (23.4), 28.1 (28.4), 35.9 (34.8), 47.0, 60.7 (60.1), 79.3, 126.8, 128.2, 132.0, 143.6, 154.4. Anal. Calcd for $C_{15}H_{20}ClNO_2$: C, 63.94; H, 7.15; N, 4.97. Found: C, 63.64; H, 7.07; N, 5.28.

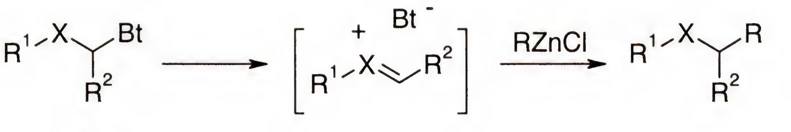
N-(*tert*-Butoxycarbonyl)-2-(phenylethynyl)pyrrolidine (**5.4e**).

Oil. Yield: 77%. ^{1}H NMR 1.50 (s, 9H), 1.82–1.99 (m, 1H), 2.01–2.24 (m, 3H), 3.36 (br s, 1H), 3.50 (br s, 1H), 4.68–4.81 (m,1H), 7.28 (s, 3H), 7.38 (s, 2H); ^{13}C NMR 23.8 (24.4), 28.5, 33.7 (33.1), 45.6, 48.7, 79.6, 81.5, 89.8, 123.1, 127.9, 128.1, 131.5, 154.1.

CHAPTER 6
REMARKABLY EASY OXIDATION OF ALKYLZINC REAGENTS IN THEIR REACTIONS WITH ELECTROPHILES TO PRODUCE ALKOXYLATED INSTEAD OF THE EXPECTED ALKYLATED PRODUCTS

6.1 Introduction

Due to their easy and high yield preparations, their functional group tolerance and high product yields, as well as the significant stereoselectivity of their reactions, organozinc reagents have been widely used in organic synthesis [91COS, 95OROS]. For example, recent studies have been devoted to the preparation of chiral alcohols by the asymmetric addition of diethylzinc to aldehydes in the presence of various enantioselective catalysts [97JA12454, 98TL2961, 99OL1095, 00JOC295]. Organozinc reagents are particularly useful in substitution reactions of benzotriazole derivatives, especially those of type **6.1**, representing masked oxoniums, thioniums or iminium salts, as documented by mutiple examples (eq. 1) [89S323, 91S69, 93T2829, 93JOC2086, 98T7167, 99JOC1979, 00JOC4364]. Although organozinc reagents are significantly less nucleophilic than Grignard reagents, they are more reactive toward benzotriazole compounds of type **6.1** due to coordination of the zinc atom at the N3 of the benzotriazole ring which enhances the leaving ability of the benzotriazole group. Moreover, highly basic Grignard and organolithium reagents can cause deprotonation at the carbon adjacent to the benzotriazole moiety which is much reduced when organozinc reagents are applied.


(eq. 1)

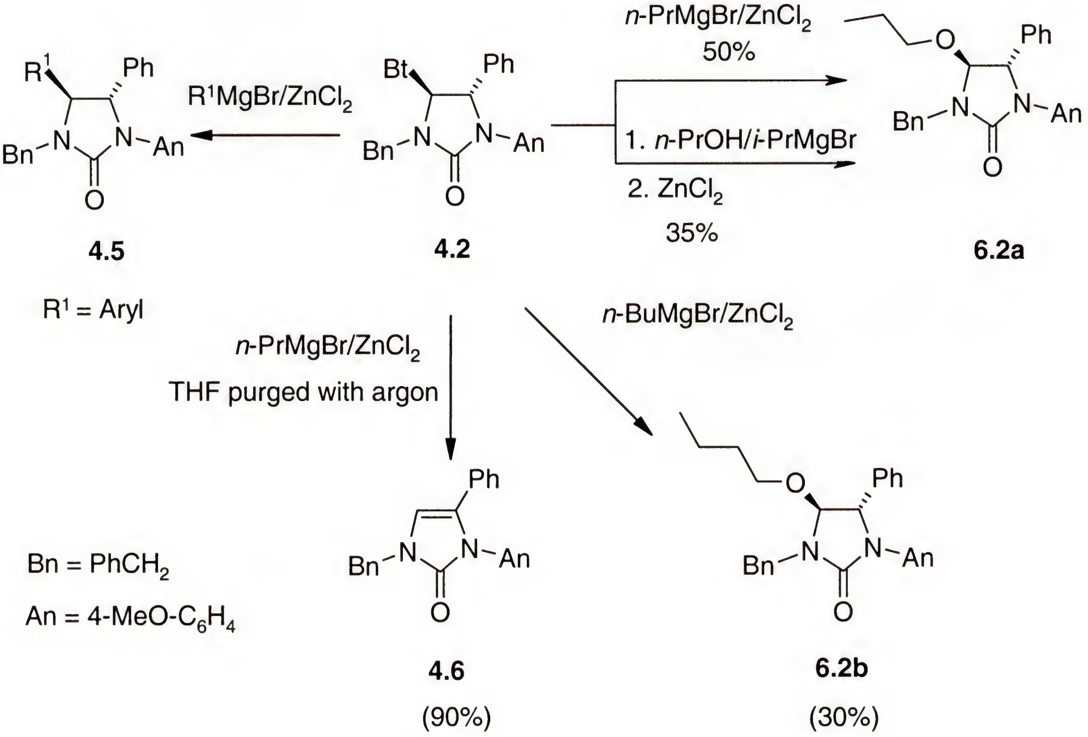
6.1

X = O , S, NBoc.

The sensitivity of organometallic reagents in general, and of organozinc reagents in particular, to air oxidation is well known [91COS211, 96OROS]. Such reactions have been previously used to prepare alcohols [97T9135], hydroperoxides [59CB2716, 65AG1074, 97T9135] and epoxides (using dialkylzinc compounds) [96AG(E)1725, 98T(A)3959, 99JOC8149]. However, in all these published procedures, to achieve the oxygen insertion, the solution of the organometallic reagent was purged with oxygen or exposed to the air; e.g. for the conversion of di(1-octyl)zinc into 1-octanol, oxygen was bubbled at 0 °C for 1 hour [97T9135]. We now report surprising and apparently novel facile oxidations of alkylzinc reagents leading to alkoxy products in good to excellent yields instead of the expected alkyl derivatives.

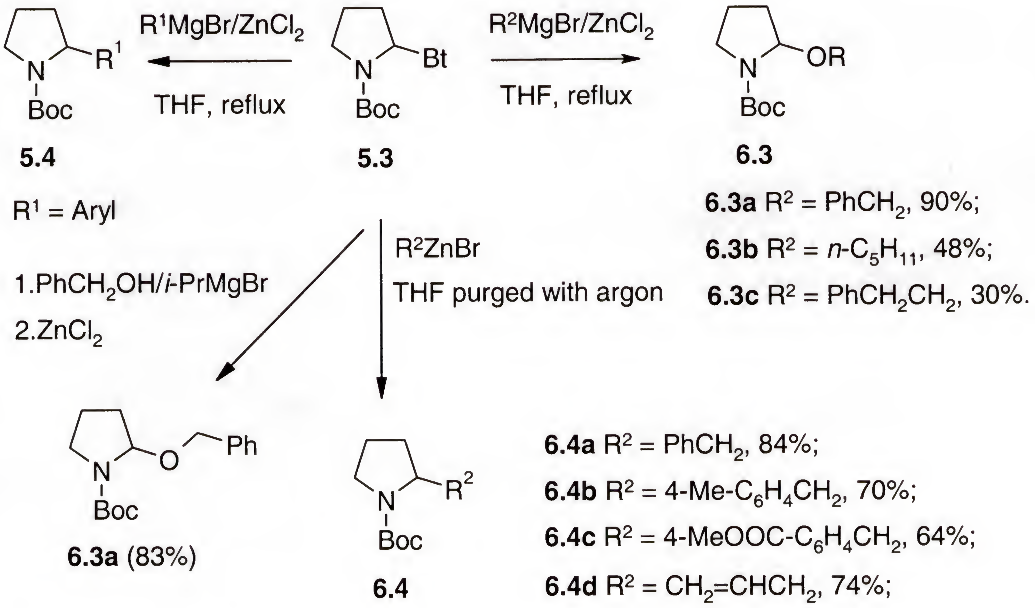
6.2 Results and Discussion

We demonstrated earlier (Chapter 4) that arylzinc reagents successfully replaced the benzotriazole moiety in *trans*-4-phenyl-5-benzotriazolylimidazolidinone (**4.2**) affording the expected products **4.5** (Scheme 6.1). We now show that, under the same reaction conditions as those previously used for arylzinc reagents, alkylzinc reagents give oxygen insertion products. Thus, **4.2** reacted with *n*-PrZnCl (generated *in situ* from *n*-PrMgBr and $ZnCl_2$) under an argon atmosphere in refluxing THF (no reaction occurred at 20 °C) to give **6.2a** (50%) together with elimination product **4.6** (30%). The structure of **6.2a** was supported by NMR spectra and HRMS; the H4/H5 coupling constant of 1.1 Hz indicated the *trans* geometry for **6.2a** [Chapter 4, 93T7787]. The structure of **6.2a** was additionally confirmed by its synthesis in 35% yield from **4.2** and *n*-PrOZnCl (generated *in situ* from *n*-PrOMgBr and $ZnCl_2$) at reflux in THF. The analogous oxygen insertion compound **6.2b** was obtained in 30% yield from **4.2** when *n*-BuZnCl was used as a nucleophile.



Scheme 6.1

We reported earlier (Chapter 5) that treatment of *N*-Boc-2-benzotriazolyl pyrrolidine **5.3** with arylzinc reagents as nucleophiles also afforded the expected 2-arylpyrrolidines **5.4** (Scheme 6.2). However, under conditions identical to those used for arylzinc halides, including conducting the reactions under an argon atmosphere, three different alkylzinc reagents once again produced only oxidation products **6.3a**-**c** in variable yields: the results are summarized in Scheme 6.2. The structures **6.3a-c** were all supported by NMR spectra and CHN analysis (or HRMS). Furthermore, the structure of **6.3a** was confirmed by its identity with the authentic **6.3a** synthesized from **5.3** and $PhCH_2OZnCl$ (generated *in situ* from $PhCH_2OMgBr$ and $ZnCl_2$).



Scheme 6.2

To avoid such oxidation, the presence of oxygen must be meticulously excluded. To achieve this, the reaction system was vacuumed at 25 °C using oil pump for about 30 minutes, then filled with argon. Argon was also bubbled through the THF solution prior to and throughout the whole reaction. Under these conditions, treatment of **4.2** with *n*-PrZnCl (generated *in situ* from *n*-PrMgBr and $ZnCl_2$) gave only the elimination product **4.6** (90% yield) and no oxidation product was observed (Scheme 6.1). This illustrated that oxygen in the reaction system indeed influences the reaction and *n*-PrZnCl (in contrast to arylzinc reagents) in this case is insufficiently nucleophilic (and/or too basic) to afford the desired substitution product of type **4.5**. However, under similar conditions, reaction of **5.3** with generated *in situ* $PhCH_2ZnCl$ (obtained from $PhCH_2MgBr$ and $ZnCl_2$) gave the desired compound **6.4a** in 84% yield (Scheme 6.2). Although **6.4a** has the same R_f value as the corresponding oxidation product **6.3a** (silica TLC plates / (CH_3CO_2Et : Hexanes = 1 : 5)), the spectra of compounds **6.3a** and **6.4a** are different. Thus, H2 appears as two broad singlet peaks in the ^1H NMR spectra of **6.4a** at 3.94 and 4.03 ppm, and C2 appears in the ^{13}C NMR spectra at 58.8 ppm. For **6.3a**, H2 signals were shown as two broad singlets at 5.30 and 5.42 ppm, and C2 appeared at 87.6 ppm. When allylzinc bromide was used as a nucleophile, the corresponding desired product **6.4d** was obtained in 74% yield from **5.3**.

The work presently described appears to possess two novel aspects: (i) the oxidation of alkylzinc reagents by very small amounts of oxygen dissolved in a solvent [86BCSJ415], and (ii) the isolation in preparatively useful yields of products with C-alkoxy groups (the nearest analogy to which appears to the isolation of 2-allylperoxy-1,2-dihydroquinolines [65AG1074].

6.3 Conclusion

In conclusion, we have discovered that easy oxidation of alkylzinc reagents in their reactions with benzotriazole derivatives can lead to C-alkoxy products in preparatively useful yields although the use of arylzinc reagents under similar reaction conditions gives the corresponding C-aryl products.

6.4 Experimental Section

General Comments. Melting points were determined on a hot stage apparatus and are uncorrected. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$

with TMS as the internal reference. THF was distilled from sodium/benzophenone. All reactions were carried out under argon atmosphere. Compounds **4.2** and **5.3** were prepared according to Chapters 4 and 5.

General Procedure for the Synthesis of Compounds **6.2a-b**, **4.6**, and **6.3a-c**. To a solution of $ZnCl_2$ (2.5 mmol, 2.5 mL 1.0 M in Et_2O) in THF (10 mL), Grignard reagent RMgBr (2.5 mmol) was added at 0 °C. Then the solution was warmed up to room temperature and stirred further for about 20 mins. Compound **4.2** or **5.3** (0.5 mmol) in THF (10 mL) was added to this organozinc reagent, and the reaction mixture was heated under reflux for 12 h. The solution obtained was cooled down to room temperature and dilute ammonium hydroxide aqueous solution was added. Then the organic layer was separated and the aqueous solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, the solvents were evaporated *in vacuo* and the residue was subjected to silica gel chromatography to give products **6.2a-b, 4.6** and **6.3a-c**, respectively.

trans-1-Benzyl-3-(4-methoxyphenyl)-4-phenyl-5-propoxyimidazolidin-2-one (**6.2a**).

yellow oil. Yield 50%. ^{1}H NMR δ 0.94 (t, *J* = 7.4 Hz, 3H), 1.55–1.62 (m, 2H), 3.30–3.33 (m, 1H), 3.43–3.48 (m, 1H), 3.72 (s, 3H), 4.19 (d, *J* = 15.1 Hz, 1H), 4.46 (d, *J* = 1.1 Hz, 1H), 4.88 (d, *J* = 1.1 Hz, 1H), 4.94 (d, *J* = 15.1 Hz, 1H), 6.77 (d, *J* = 9.1 Hz, 2H), 7.19–7.32 (m, 10H), 7.37 (d, *J* = 9.1 Hz, 2H). ^{13}C NMR δ 10.7, 23.0, 44.6, 55.4, 65.0, 67.8, 90.1, 114.0, 121.3, 125.9, 127.4, 128.0, 128.2, 128.5, 129.1, 132.0, 136.9, 138.6, 155.5, 156.8. HRMS Calcd for $C_{26}H_{29}N_2O_3$: 417.2178 (M+1). Found: 417.2178 (M+1).

trans-1-Benzyl-5-butoxy-3-(4-methoxyphenyl)-4-phenylimidazolidin-2-one (**6.2b**).

yellow oil. Yield 30%. ^{1}H NMR δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.34–1.42 (m, 2H), 1.45–1.57 (m, 2H), 3.34–3.39 (m, 1H), 3.46–3.52 (m, 1H), 3.73 (s, 3H), 4.19 (d, *J* = 15.1 Hz, 1H), 4.46 (d, *J* = 1.2 Hz, 1H), 4.88 (d, *J* = 1.2 Hz, 1H), 4.96 (d, *J* = 15.1 Hz, 1H), 6.77 (d, *J* = 9.1 Hz, 2H), 7.18–7.32 (m, 10H), 7.37 (d, *J* = 9.1 Hz, 2H). ^{13}C NMR δ 13.9, 19.3, 31.8, 44.6, 55.4, 65.1, 65.9, 90.1, 114.0, 121.3, 125.9, 127.4, 128.0, 128.2, 128.5, 129.1, 132.1, 136.9, 138.6, 155.5, 156.8. HRMS Calcd for $C_{27}H_{31}N_2O_3$: 431.2335 (M+1). Found: 431.2348 (M+1).

1-Benzyl-3-(4-methoxyphenyl)-4-phenyl-1,3-dihydro-2*H*-imidazol-2-one (**4.6**) [Chapter 4].

white needles, m.p. 95–96 °C (from hexanes and methylene chloride). ^{1}H NMR δ 3.79 (s, 3H), 4.90 (s, 2H), 6.32 (s, 1H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.99–7.02 (m, 2H), 7.13–7.17 (m, 5H), 7.34–7.38 (m, 5H). ^{13}C NMR δ 47.3, 55.4, 108.8, 114.2, 124.2, 126.9, 127.2, 127.9, 128.2, 128.3, 128.4, 128.8, 129.4, 136.7, 153.4, 158.4.

tert-Butyl 2-(Benzyloxy)-1-pyrrolidinecarboxylate (**6.3a**).

yellow oil. Yield 90%. ^{1}H NMR δ 1.48 and 1.51 (2 s, 9H), 1.68–2.10 (m, 4H), 3.27–3.47 (m, 2H), 4.50–4.69 (m, 2H), 5.30 and 5.42 (2 br s, 1H), 7.15-7.32 (m, 5H). ^{13}C NMR δ 21.7 (22.6), 28.3 (28.4), 32.9 (32.4), 45.8 (45.3), 69.8 (70.2), 79.4 (79.9), 87.3, 127.1, 127.3, 128.1 (128.2), 139.0 (138.5), 155.1 (154.1). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.60; H, 8.43; N, 5.20.

tert-Butyl 2-(Pentyloxy)-1-pyrrolidinecarboxylate (**6.3b**).

yellow oil. Yield 48%. ^{1}H NMR δ 0.89 (m, 3H), 1.31 (m, 4H), 1.46 and 1.47 (2 s, 9H), 1.68–2.05 (m, 4H), 3.29–3.51 (m, 4H), 5.11 and 5.24 (2 br s, 1H). ^{13}C NMR δ 14.0, 21.8, 22.5, 22.7, 28.4 (28.5), 29.6, 32.9 (32.3), 45.9 (45.3), 67.9 (68.3), 79.8 (79.4), 87.3, 155.1 (154.2). Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.57; N, 5.44. Found: C, 65.44; H, 10.92; N, 5.55.

tert-Butyl 2-(phenethyloxy)-1-pyrrolidinecarboxylate (**6.3c**).

yellow oil. Yield 30%. ^{1}H NMR δ 1.45 (s, 9H), 1.72–2.03 (m, 4H), 2.86 (t, $J = 7.1$ Hz, 2H), 3.32–3.40 (m, 2H), 3.76–3.82 (m, 2H), 5.14 and 5.29 (2 br s, 1H), 7.20–7.27 (m, 5H); ^{13}C NMR δ 21.7 (22.7), 28.4, 32.3 (32.9), 36.4, 45.8 (45.3), 68.6 (68.8), 79.5 (79.8), 87.2 (87.4), 125.9, 128.1, 128.7 (128.9), 139.1 (139.2), 154.2 (155.1). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.76; H, 8.99; N, 4.50.

Synthesis of *tert*-Butyl 2-Benzyl-1-pyrrolidinecarboxylate (**6.4a**). The 100 mL round-bottom flask was vacuumed for around 30 min using oil pump, then filled with argon. The solution of $ZnCl_2$ (2.5 mmol, 2.5 mL 1.0 M in Et_2O) was added to THF (10 mL) in the above flask. After argon was bubbled through the solution for 15 min, $PhCH_2MgBr$ (2.5 mmol, 1.0 M in THF) was added at 0°C, then the solution was warmed up to room temperature and stirred further for about 20 min under continuous bubbling argon through the solution. Compound **5.3** (0.5 mmol) in THF (10 mL) was added to the above prepared solution of organozinc reagent, then the mixed solution was further purged with argon for 15 min at room temperature. Next the reaction solution was heated under reflux for 12 h under argon atmosphere. The solution was cooled down to room temperature and dilute ammonium hydroxide aqueous solution was added. Then the organic layer was separated and the aqueous solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, the solvents were evaporated *in vacuo* and the residue was subjected to silica gel chromatography to give **6.4a** [92T8253] as yellow oil in 84% yield. ^{1}H NMR δ 1.51 (s, 9H), 1.62–1.75 (m, 4H), 2.48-2.55 (m, 1H), 3.03–3.18 (m, 1H), 3.28 (br s, 1H), 3.36 (br s, 1H), 3.94 and 4.03 (2 br s, 1H), 7.18–7.29 (m, 5H). ^{13}C NMR δ 22.6 (23.4), 28.6, 29.6 (28.8), 40.5 (39.5), 46.3 (46.8), 58.8, 79.2 (79.0), 126.2, 128.4, 129.4 (129.5), 139.2, 154.5.

General Procedure for the Synthesis of Compounds (**6.4b-d**). The 100 mL round-bottom flask containing activated zinc powder (4.5 mmol, 293 mg) was vacuumed for around 30 min using oil pump, then filled with argon. Then THF (10 mL) was added into the above flask. After argon was bubbled through THF solution for 15 min, RBr (3 mmol) in THF (10 mL) was added at room temperature and the reaction mixture was stirred for about 15 min under continuous bubbling argon through the solution. Then the above solution was heated under reflux for 10 hours under argon and cooled down to room temperature. The solution was decanted and transferred to another 100 mL round-bottom flask which had been vacuumed and filled with argon. Compound **5.3** (0.5 mmol) in THF (10 mL) was added to the above clear solution of organozinc reagent, then the mixed solution was further purged with argon for 15 min at room temperature. Next the reaction solution was heated under reflux for 12 h under argon atmosphere. The solution was cooled down to room temperature and dilute ammonium hydroxide aqueous solution was added. Then the organic layer was separated and the aqueous solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, the solvents were evaporated *in vacuo* and the residue was subjected to silica gel chromatography to give **6.4b-d**, respectively.

tert-Butyl 2-(4-Methylbenzyl)-1-pyrrolidinecarboxylate (**6.4b**).

yellow oil. Yield 70%. ^{1}H NMR δ 1.72 (s, 9H), 1.90–1.98 (m, 4H), 2.53 (s, 3H), 2.65–2.72 (m, 1H), 3.20–3.36 (m, 1H), 3.49 (br s, 1H), 3.57 (br s, 1H)), 4.12 and 4.21 (2 br s, 1H), 7.25–7.47 (m, 4H). ^{13}C NMR δ 21.0, 22.6 (23.4), 28.6, 29.5, 40.1 (39.1), 46.3 (46.8), 58.9, 79.2 (79.0), 129.0, 129.2, 129.4, 136.0, 154.5. Anal. Calcd for $C_{17}H_{25}NO_2$: N, 5.09. Found: N, 5.28.

tert-Butyl 2-[4-(Methoxycarbonyl)benzyl]-1-pyrrolidinecarboxylate (**6.4c**).

yellow oil. Yield 64%. ^{1}H NMR δ 1.46 and 1.50 (2 s, 9H), 1.67–1.75 (m, 4H), 2.61–2.67 (m, 1H), 3.17–3.22 (m, 1H), 3.28–3.36 (m, 2H), 3.91 (s, 3H), 3.96 and 4.02 (2 br s, 1H), 7.22–7.29 (m, 2H), 7.95–7.97 (m, 2H). ^{13}C NMR δ δ 22.6 (23.4), 28.6, 29.7 (28.9), 40.7 (39.6), 46.3 (46.8), 52.0, 58.5, 79.4 (79.2), 129.4, 129.6, 129.8, 144.7, 154.5, 167.1. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.28; H, 8.20; N, 4.61.

tert-Butyl 2-Allyl-1-pyrrolidinecarboxylate (**6.4d**) [92T8253].

yellow oil. Yield 74%. ^{1}H NMR δ 1.40 (s, 9H), 1.46–1.80 (m, 4H), 2.02–2.09 (m, 1H), 2.34–2.46 (m, 1H), 3.24 (br s, 2H), 3.69 and 3.77 (2 br s, 1H), 4.95–5.01 (m, 2H), 5.64–5.72 (m, 1H). ^{13}C NMR δ 22.9 (23.6), 28.5 (28.4), 29.7 (30.1), 39.0 (38.2), 46.3 (46.7), 56.7, 79.0, 117.0, 135.3, 154.5.

CHAPTER 7
CONCLUSION

A study of benzotriazole as an organic auxiliary for the preparations of a variety of hetereocycles is reported. It includes the synthesis of functionized piperidines using both carbocation and radical chemistry, stereoselective synthesis of *trans* 4,5-disubstituted imidazolidin-2-ones and facile preparations of 2-substituted *N*-Boc-pyrrolidines using benzotriazole-assisted formation of dipole-stabilized carbanions α to the nitrogen atom.

In the course of the synthesis of functionalized piperidines using *N,N*-bis[(benzotriazol-1-yl)methyl]amines as 1,3 –dication equivalents, *N,N*-bis[(benzotriazol-1-yl)methyl]anilines were converted into julolidine analogues.

During the synthesis of substituted piperidines using 6-exo-α-aminoalkyl radical cycloaddition reactions, [1,2]-aza-Wittig rearrangements were uncovered and further studied using SmI_2 as a reducing reagent.

It was discovered that alkylzinc reagents were remarkably easily oxidized during the synthesis of *trans* 4,5-disubstituted imidazolidin-2-ones and 2-substituted *N*-Boc-pyrrolidines. Non-oxidized products could be obtained by bubbling argon to purge the reaction solutions.

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Each time a reference is cited, a number and letter code appear in brackets, for example [00ABC000]. The first two digits denote the year of the twentieth century, the letter code is an abbreviation for the journal or book cited and the last digits represent the page number. Additional notes to this reference system are as follows:

(i) References are listed consecutively by year, alphabetically by the journal code and then by page number.

(ii) Each reference code is followed by the conventional literature citation complete with the name of the authors.

(iii) Journals which are published in more than one part, or more than one volume per year, include in the abbreviation cited the appropriate part or volume number.

(iv) Books and journals which are less commonly used are called "MT" for miscellaneous.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of the Doctor of Philosophy.

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